TOXICOLOGICAL PROFILE FOR
ETHYLENE GLYCOL AND PROPYLENE GLYCOL

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

September 1997

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Technical Report for ethylene glycol and propylene glycol was released in May 1993. This edition supersedes any previously released draft or final profile or report.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

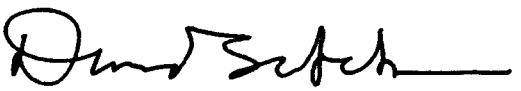
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



David Satcher, M.D., Ph.D.
Administrator
Agency for Toxic Substances and
Disease Registry

*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). Section 211 of SARA also amended Title 10 of the U. S. Code, creating the Defense Environmental Restoration Program. Section 2704(a) of Title 10 of the U. S. Code directs the Secretary of Defense to notify the Secretary of Health and Human Services of not less than 25 of the most commonly found unregulated hazardous substances at defense facilities. Section 2704(b) of Title 10 of the U. S. Code directs the Administrator of the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare a toxicological profile for each substance on the list provided by the Secretary of Defense under subsection (b).

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHORS(S):

Ed Murray, Ph.D.
ATSDR, Division of Toxicology, Atlanta, GA

Julia George, Ph.D.
Research Triangle Institute, Research Triangle Park, NC

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures consistency with ATSDR policy.

2. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MI&s), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

4. Quality Assurance Review. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been followed.

PEER REVIEW

A peer review panel was assembled for ethylene glycol and propylene glycol. The panel consisted of the following members:

1. Dr. Gregory Grauer, Associate Professor, Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, Colorado;

2. Dr. Philip Leber, Private Consultant, Chem-Tox Consulting, Akron, Ohio; and

3. Dr. Kenneth McMartin, Professor, Department of Pharmacology and Therapeutics, Section of Toxicology, Louisiana State University Medical Center, Shreveport, Louisiana.

These experts collectively have knowledge of ethylene glycol and propylene glycol's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list.of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. PUBLIC HEALTH STATEMENT

This statement was prepared to give you information about ethylene glycol and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,416 hazardous waste sites as the most serious in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up activities. Ethylene glycol has been found in at least 34 of the sites on the NPL. However, we do not know how many of the 1,416 NPL sites have been evaluated for ethylene glycol. As EPA evaluates more sites, the number of sites at which ethylene glycol is found may increase. This information is important for you to know because ethylene glycol may cause harmful health effects and because these sites are potential or actual sources of human exposure to ethylene glycol. Propylene glycol is a chemical that has physical and chemical properties that are similar to ethylene glycol, but it does not cause the same human health effects. Propylene glycol can be used in many of the same products that contain ethylene glycol. Propylene glycol has been identified in at least 5 of the 1,416 NPL sites. The information describing propylene glycol is important for you to know so that you may distinguish between exposure to ethylene glycol and exposure to propylene glycol.

When a chemical is released from a large source, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous chemical such as ethylene glycol, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact),

the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, lifestyle, and state of health.

1.1 WHAT ARE ETHYLENE GLYCOL AND PROPYLENE GLYCOL?

Ethylene glycol is a synthetic liquid substance that absorbs water. Ethylene glycol is used to make antifreeze and de-icing solutions for cars, airplanes, and boats. It is an ingredient in hydraulic brake fluids and in inks used in stamp pads, ballpoint pens, and print shops. It is a, solvent used in the paint and plastics industry, and is used to produce polyester fibers. Other names for ethylene glycol are 1,2-dihydroxyethane, 1,2-ethanediol, 2-hydroxyethanol, ethylene alcohol, glycol, and ethylene dihydrate.

Propylene glycol is also a synthetic liquid substance that absorbs water. Like ethylene glycol, propylene glycol is also used to make polyester compounds, and as a base for de-icing solutions. Propylene glycol is used by the chemical, food, and pharmaceutical industries as an antifreeze when leakage might lead to contact with food. The Food and Drug Administration (FDA) has classified propylene glycol as an additive that is “generally recognized as safe” for use in food. It is used to absorb extra water and maintain moisture in certain medicines, cosmetics, or food products. It is a solvent for food colors and flavors, and in the paint and plastics industries. Propylene glycol is also used to create artificial smoke or fog used in fire-fighting training and in theatrical productions. Other names for propylene glycol are 1,2-dihydroxypropane, 1,2-propanediol, methyl glycol, and trimethyl glycol.

Both ethylene glycol and propylene glycol are clear, colorless, slightly syrupy liquids at room temperature. Either compound may exist in air in the vapor form, although propylene glycol must be heated or briskly shaken to produce a vapor. Ethylene glycol is odorless but has a sweet taste. Propylene glycol is practically odorless and tasteless.

In this profile, ethylene glycol and propylene glycol are discussed together because they have very similar structures and physical properties, and can be used for many of the same

purposes, although their toxic properties are very different. For more information on the sources, properties, and uses of ethylene glycol and propylene glycol, see Chapters 3 and 4.

1.2 WHAT HAPPENS TO ETHYLENE GLYCOL AND PROPYLENE GLYCOL WHEN THEY ENTER THE ENVIRONMENT?

Waste streams from the manufacture of ethylene glycol and propylene glycol are primarily responsible for the releases of both compounds into the air, water, and soil. Ethylene glycol and propylene glycol can enter the environment when they are used as runway and aircraft de-icing agents. They can also enter the environment through the disposal of products that contain them. Neither compound is likely to exist in large amounts in the air. We have little information about what happens to ethylene glycol and propylene glycol in the air. The small amounts of ethylene glycol and propylene glycol that may enter the air are likely to break down quickly. If either chemical escapes into the air, it will take between 24 and 50 hours for half the amount released to break down. Both compounds can mix completely with water and can soak into soil. Both ethylene glycol and propylene glycol can break down relatively quickly (within several days to a week) in surface water and in soil. Ethylene glycol and propylene glycol can also travel from certain types of food packages into the food in the package. See Chapters 4 and 5 for more information on ethylene glycol and propylene glycol in the environment.

1.3 HOW MIGHT I BE EXPOSED TO ETHYLENE GLYCOL AND PROPYLENE GLYCOL?

The general population can be exposed to ethylene glycol because it is found in common products such as antifreeze, photographic developing solution, coolants, and brake fluid. Ethylene glycol represents a very small part (less than 1%) of photographic developing solutions, so you are not likely to be exposed to it in any significant quantity when using these solutions. If you come into contact with automotive fluids such as antifreeze, coolants, and brake fluid, you may be exposed to ethylene glycol. Ethylene glycol is less than 0.1% of brake fluid, so brake fluid presents little, if any, risk of exposure. People who work in

industries that use ethylene glycol may be exposed by touching these products or inhaling mists from spraying them. These exposures tend to be at low levels, however. For instance, in areas where de-icing fluids were sprayed, ethylene glycol vapor has been found in the air at low concentrations ranging from less than 0.02 parts per million parts of air (parts per million or ppm) to 4.1 ppm. According to the guidelines set by the American Conference of Governmental Industrial Hygienists (ACGIH), the maximum allowable level of ethylene glycol in workplace air is 50 ppm. Except for operations where ethylene glycol has been sprayed or made into a mist or vapor, exposure to it in the air is unlikely. High doses that could produce harmful effects usually result from intentionally or accidentally eating or drinking a certain amount at one time. The small amounts of ethylene glycol that you might breathe in or get on your skin when using these products are very unlikely to harm you.

Propylene glycol has been approved for use at certain levels in food, cosmetics, and pharmaceutical products. If you eat food products, use cosmetics, or take medicines that contain it, you will be exposed to propylene glycol, but these amounts are not generally considered harmful. People who work in industries that use propylene glycol may be exposed by touching these products or inhaling mists from spraying them. These exposures tend to be at low levels, however. Propylene glycol is used to make artificial smoke and mists for fire safety training, theatrical performances, and rock concerts. These artificial smoke products may also be used by private citizens. These products are frequently used in enclosed spaces, where exposure may be more intense.

See Chapter 5 for more information on exposure to ethylene glycol and propylene glycol.

1.4 HOW CAN ETHYLENE GLYCOL AND PROPYLENE GLYCOL ENTER AND LEAVE MY BODY?

Ethylene glycol or propylene glycol can enter your bloodstream if you breathe air containing mists or vapors from either compound. Both compounds can also enter your bloodstream through your skin if you come in direct contact with them and do not wash them off. If you eat products that contain propylene glycol, it may enter your bloodstream. Exposure of the

general population to ethylene glycol is usually limited to people who work on cars or use photographic developing solutions. Most fatal ethylene glycol poisonings occur after intentionally eating or drinking it. People and animals can also be poisoned by eating or drinking antifreeze solutions that have not been properly stored or disposed of. Many of the people exposed to ethylene glycol are exposed in their workplaces or while changing antifreeze, brake fluids, or coolants in their cars. However, other people can accidentally be exposed when these auto products are not disposed of properly. Exposure of the general population to propylene glycol is more likely since many foods, drugs, and cosmetics contain it.

Studies of people and animals show that ethylene glycol enters the body quickly and breaks down very quickly. These studies have shown that ethylene glycol is no longer found in urine or body tissues 48 hours after exposure. Propylene glycol breaks down at about the same rate as ethylene glycol. However, studies of people and animals show that if you have repeated eye, skin, nasal, or oral exposures to propylene glycol for a short time, you may develop some irritation.

1.5 HOW CAN ETHYLENE GLYCOL AND PROPYLENE GLYCOL AFFECT MY HEALTH?

Exposure to ethylene glycol can remove water from the tissues in your body and cause loss of body water in the form of urine. If you drink ethylene glycol, it will spread evenly throughout your body within a few hours. Within 24-48 hours of drinking ethylene glycol, much of the compound will be excreted unchanged in the urine and the rest will completely break down so that it can no longer be detected in your body. When ethylene glycol breaks down in the body, it forms chemicals that crystallize; the crystals collect in your body and can affect kidney function. It can also form chemicals that are acidic, thus changing the body’s acid/base balance. Swallowing a certain amount of ethylene glycol can kill you. Studies show that swallowing ethylene glycol causes very similar effects in people and animals. The very small amounts of ethylene glycol that could be tasted or otherwise accidentally eaten (for example, by putting your fingers in your mouth) in situations other

than intentionally or accidentally drinking ethylene glycol are not likely to cause serious illness or death. Moreover, in cases that involve eating or drinking large amounts of ethylene glycol, antidotal treatment after early diagnosis has been very successful.

Propylene glycol breaks down at the same rate as ethylene glycol, although it does not form harmful crystals when it breaks down. Frequent skin exposure to propylene glycol can sometimes irritate the skin.

1.6 ARE THERE MEDICAL TESTS TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ETHYLENE GLYCOL OR PROPYLENE GLYCOL?

Tests are available to determine if you have been exposed to ethylene glycol. These tests are only used on people who are showing symptoms of ethylene glycol poisoning (but they could be used in other situations). The tests are most often used on people who have intentionally consumed, or who suspect they have consumed, large amounts of ethylene glycol. Recently, tests have been developed that can detect ethylene glycol in blood in 30 minutes. These tests are successful only if you have recently been exposed to large amounts of ethylene glycol. Propylene glycol is generally considered to be a safe chemical, and is not routinely tested for, unless specific exposure, such as to a medicine or cosmetic, can be linked with the observed bad symptoms. Since both ethylene glycol and propylene glycol break down very quickly in the body, they are very difficult to detect even though the symptoms may be present. Refer to Chapters 2 and 6 for more information on these tests.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The government has developed regulations and guidelines for ethylene glycol arid propylene glycol. These are designed to protect the public from potential adverse health effects.

The Occupational Safety and Health Administration (OSHA) regulates levels of ethylene glycol in the workplace. The maximum allowable amount of ethylene glycol in workroom air

is 50 ppm, based on the guidelines of the ACGIH. The EPA has set a drinking water guideline for ethylene glycol of 7,000 micrograms in a liter of water, and has proposed that a release into the environment need not be reported under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund) or the Emergency Planning Community Right-to-Know Act unless it exceeds 5,000 pounds within 24 hours.

The Food and Drug Administration (FDA) has classified propylene glycol as "generally recognized as safe," which means that it is acceptable for use in flavorings, drugs, and cosmetics, and as a direct food additive. According to the World Health Organization, the acceptable dietary intake of propylene glycol is 25 mg of propylene glycol for every kilogram (kg) of body weight. For more information on the regulations and guidelines that apply to ethylene glycol and propylene glycol, see Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, Georgia 30333
(404) 639-6000

This agency can also provide you with the location of the nearest occupational and environmental health clinic. These clinics specialize in the recognition, evaluation, and treatment of illnesses resulting from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of ethylene glycol and propylene glycol and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for ethylene glycol and propylene glycol based on toxicological studies and epidemiological investigations.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

The general population may be exposed to either ethylene glycol or propylene glycol. Although the two compounds are similar in structure and chemical characteristics, they do not share the same degree of toxicity. The two compounds are presented together in this document because they share common physical properties, and can be used interchangeably in a number of industrial applications. Ethylene glycol is widely sold in grocery stores and in automobile supply, discount, drug, and other stores throughout the United States for general use as an antifreeze/coolant in automobile radiators. Additionally, it is used in the manufacturing or blending of polyester products; aircraft and runway de-icing fluids; heat transfer fluids used in heating, ventilation, and air conditioning systems; polyester resins; humectants; alkyd-type resins; plasticizers; electrolytic capacitors; low freeze dynamite; and brake and shock solutions (Wiener and Richardson 1988). Ethylene glycol is also used in the production of artificial mists or fogs (NIOSH 1994). Propylene glycol is designated as a Generally Recognized As Safe (GRAS) additive by the Food and Drug Administration (FDA) and is widely used in commercial formulations of foods, drugs, and cosmetics (Morshed et al. 1988). Propylene glycol is used as a de-icer, and in heat transfer fluids. It is also an ingredient of many products that are used to produce artificial smoke or mist for theatrical productions, fire safety training, or rock concerts.

Of the two glycols, ethylene glycol exhibits a much higher degree of toxicity than propylene glycol. Toxicity information for each compound is presented separately, within sections, below.

2. HEALTH EFFECTS

Dermal exposure, through activities such as changing antifreeze, is the most likely route of exposure to ethylene glycol, but dermal exposure is not likely to lead to toxic effects. Only oral exposure, through accidental or intentional ingestion, is likely to lead to such effects, and then only if a sufficient amount is swallowed at one time. A review of the literature for ethylene glycol indicated that the stages of oral ethylene glycol poisoning in humans are well understood and documented. There is adequate knowledge of ethylene glycol metabolism to permit successful treatment of ethylene glycol intoxication, and substantial information concerning pathology and pathophysiology of the organ systems involved is available. Although the majority of the studies in humans represent descriptions of case studies of accidental or intentional poisoning, or exposure in industrial settings, they have been collected for a period of over 60 years. Animal studies corroborate human findings and were used to provide quantitative data to support observations made in humans.

Oral exposure to the small amounts of propylene glycol found in foods and drugs is unlikely to cause toxic effects. Dermal exposure to propylene glycol, through cosmetics or drugs, or inhalation of synthetic smoke or mist, may be more frequently associated with reported reactions. Propylene glycol induces remarkably fewer adverse effects in both humans and animals than does ethylene glycol. Data describing either human or animal effects after exposure to propylene glycol were not as prevalent as those found for ethylene glycol. Human data came from case reports of clinical studies, adverse reactions to medical treatment, or accidental exposure. Animal data generally support those effects, or lack thereof, observed in humans.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites or other areas where they may be exposed to ethylene glycol or propylene glycol, the information in this section is organized by chemical, and then by health effect-death, systemic, immunological and lymphoreticular, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods-acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowestobserved-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the

studies. LOAELs have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgement may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to,classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. These distinctions are intended to help the users of this document identify the levels of exposure at which adverse health effects start to appear. LOAELs or NOAELs should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these differences to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user’s perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites or other sites of exposure may want information on levels of exposure associated with more subtle effects in humans or animals or exposure levels below which no adverse effects have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for both ethylene glycol and propylene glycol. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify target organs(s) of effect or the most sensitive health effects(s) for a specific duration within a given route of exposure. MRLs are based on noncancer health effects only and do not reflect a consideration of carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure. Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), uncertainties are associated with these

techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for heahh effects that are delayed in development or result from repeated acute insuhs, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

Information regarding health effects of ethylene glycol following inhalation exposure is Iimited. Health effects in humans were found in only a few studies (Bond et al. 1985; Triosi 1950; Wills et al. 1974). Animal studies were described by Tyl (1985, 1988a). Information regarding health effects of propylene glycol following inhalation exposure is also limited. No studies of health effects in humans were found. Studies in animals were few (Konradova et al. 1978; Robertson et al. 1947; Suber et al. 1989).

2.2.1.1 Death

No studies were located regarding death in humans or animals after inhalation exposure to ethylene glycol. Therefore, no LOAELs for death following inhalation exposure could be established. Based on the absence of data in the literature, it is unlikely that sufficient amounts of ethylene glycol would be present or inhaled near hazardous waste sites to cause death among people living in the area.

No studies were located regarding death in humans following inhalation exposure to propylene glycol. Twenty-nine monkeys were continuously exposed to propylene glycol vapor over a period of 13 months, at doses of 32-112 ppm (doses not further specified) (Robertson et al. 1947). Thirteen of the monkeys died or were killed when ill during the course of the experiment (Robertson et al. 1947). Based on the relative lack of data in the literature, it is unlikely that sufficient amounts of propylene glycol would be present or inhaled near hazardous waste sites to cause death among people living in the area.

The LOAEL value from the study by Robertson et al. (1947) for death in monkeys after inhalation exposure to propylene glycol is recorded in Table 2-2 and plotted Figure 2-2.

2.2.1.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, musculoskeletal, hepatic, endocrine, dermal, ocular, body weight, or metabolic effects in humans or respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, endocrine, dermal, ocular, or metabolic effects in animals after inhalation exposure to ethylene glycol. No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, body weight, or metabolic effects in humans, or cardiovascular, musculoskeletal, dermal, ocular, or metabolic effects in animals after inhalation exposure to propylene glycol. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category for ethylene glycol after inhalation exposure are reported in Table 2-l and plotted in Figure 2-l. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category for propylene glycol after inhalation exposure are reported in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. Throat and upper respiratory tract irritation was observed after 1.5 minutes of inhalation exposure of volunteers exposed to a concentration of 55 ppm ethylene glycol (Wills et al. 1974). Doses above 79 ppm were very irritating and were not tolerated for more than 1 minute (Wills et al. 1974). Because of the low vapor pressure of ethylene glycol, however, the potential inhalation hazard in the vicinity of a hazardous waste site is considered to be low (Siew et al. 1975a), although small quantities of ethylene glycol could be inhaled in contaminated dust.

Studies assessing adverse respiratory effects after acute or intermediate inhalation exposure of animals to propylene glycol are inconclusive. The effects of acute inhalation exposure to 10% concentrations of propylene glycol for 20 and 120 minutes in rabbits showed an increased number of degenerated goblet cells in tracheal lining (Konradova et al. 1978). However, the observations made in rats after an intermediate inhalation exposure to propylene glycol did not support those findings. Rats which inhaled 321 ppm of propylene glycol over 90 days had thickened respiratory epithelium with enlarged goblet cells (Suber et al. 1989). Nasal hemorrhaging was also present in rats exposed to a lower dose of 51 ppm propylene glycol, probably caused by dehydration. In rhesus monkeys and rats, continuous

TABLE 2-1. Levels of Significant Exposure to Ethylene Glycol - Inhalation

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
ACUTE EXPOSURE							
Systemic							
1	Human	15 min	Resp		55 M (throat and upper respiratory tract irritation)		Wills et al. 1974
2	Rat (CD)	10 d Gd 6-15 6 hr/d	Hepatic	400 F	1000 F (increased absolute and relative liver weight)		Tyl 1985
			Renal	1000 F			
			Bd Wt	1000 F			
3	Mouse (CD-1)	10 d Gd 6-15 6 hr/d	Hepatic	1000 F			Tyl 1985
			Renal	1000 F			
			Bd Wt	60 F	400 F (reduced body weight and weight gain)		
4	Mouse (CD-1)	10 d Gd 6-15 6 hr/d	Hepatic	985 F			Tyl 1988a
			Renal	197[b] F	394 F (increased absolute kidney weight)		
			Bd Wt	985 F			
5	Mouse (CD-1)	10 d Gd 6-15 6 hr/d	Hepatic	827 F			Tyl 1988a
			Renal	827 F			
			Bd Wt		827 F (reduced maternal weight gain)		
Reproductive							
6	Rat (CD)	10 d Gd 6-15 6 hr/d		1000			Tyl 1985

TABLE 2-1. Levels of Significant Exposure to Ethylene Glycol - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
7	Mouse (CD-1)	10 d Gd 6-15 6 hr/d		60			400	(postimplantation loss)	Tyl 1985
8	Mouse (CD-1)	10 d Gd 6-15 6 hr/d		985					Tyl 1988a
9	Mouse (CD-1)	10 d Gd 6-15 6 hr/d					827	(postimplantation loss)	Tyl 1988a
Developmental									
10	Rat (CD)	10 d Gd 6-15 6 hr/d		60	400	(reduced ossification of the humerus, zygomatic arch, and metatarsals and proximal phalanges of the hindlimb)			Tyl 1985
11	Mouse (CD-1)	10 d Gd 6-15 6 hr/d		60	400	(decreased fetal body weight, increased incidence of variations)			Tyl 1985
12	Mouse (CD-1)	10 d Gd 6-15 6 hr/d		394	985	(reduced fetal body weight; increased skeletal variations)			Tyl 1988a
13	Mouse (CD-1)	10 d Gd 6-15 6 hr/d			827	(reduced fetal body weight; increased skeletal variations)			Tyl 1988a
INTERMEDIATE EXPOSURE									
Systemic									
14	Human	30 d 20-22 hr/d	Hemato Renal	19 M 19 M					Wills et al. 1974

TABLE 2-1. Levels of Significant Exposure to Ethylene Glycol - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
	Neurological						
15	Human	30 d 20-22 hr/d			19M (slight headache, low backache)		Wills et al. 1974

[a]The number corresponds to entries in Figure 2-1.

[b]Used to derive an acute inhalation minimal risk level (MRL) of 0.5 ppm; NOAEL was multiplied by an exposure factor of 6/24 hours, and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability)

Bd Wt = body weight; d = day(s); F = female; Gd = gestational day; Hemato = hematological; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; M = male; min = minute(s); NOAEL = no-observable-adverse-effect level; Resp = respiratory; wk = week(s)

Figure 2-1. Levels of Significant Exposure to Ethylene Glycol - Inhalation

Acute (≤14 days)

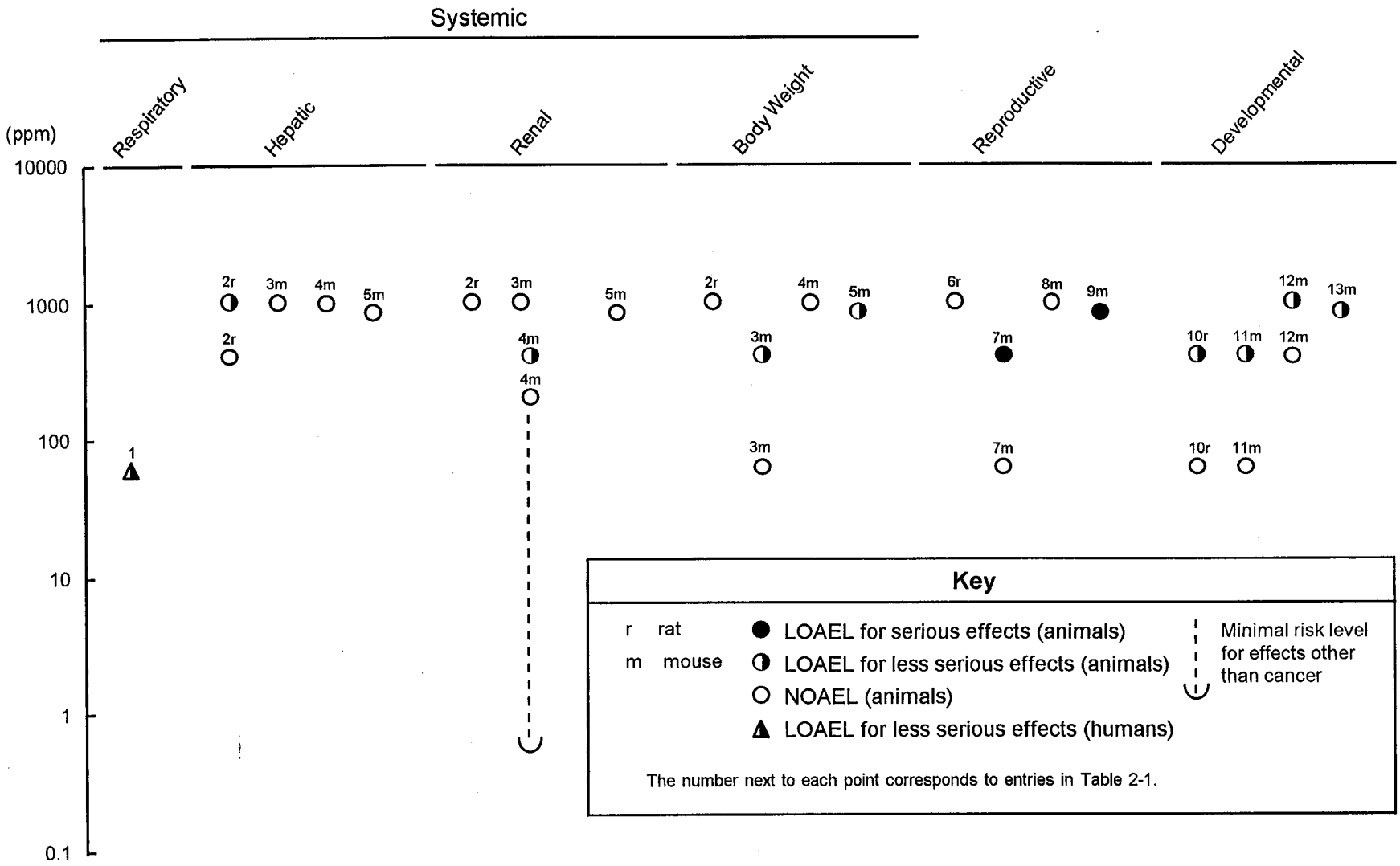


Figure 2-1. Levels of Significant Exposure to Ethylene Glycol - Inhalation (continued)

Intermediate (15-364 days)

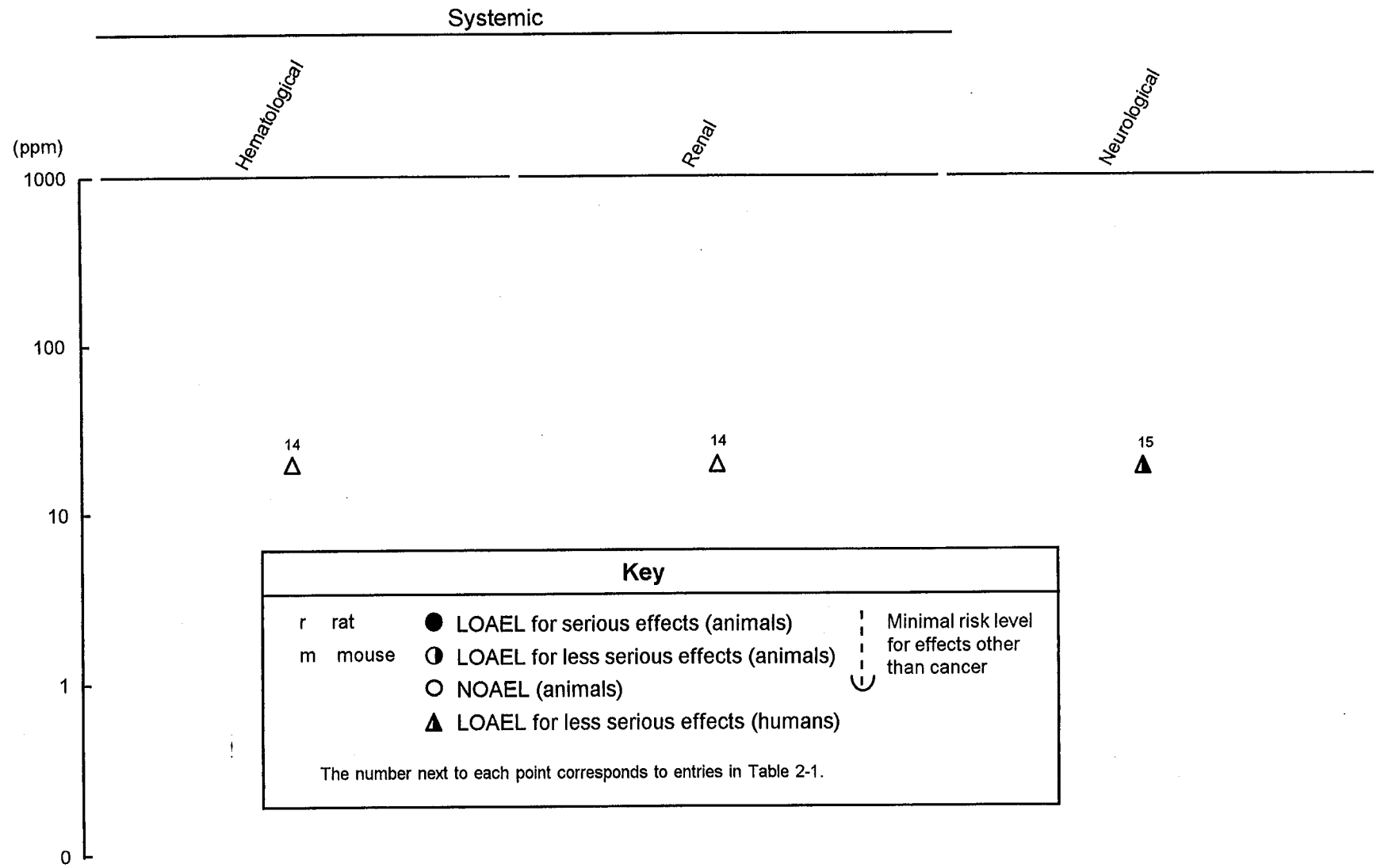


TABLE 2-2. Levels of Significant Exposure to Propylene Glycol - Inhalation

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
Systemic							
1	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d	Resp		51[b] (nasal hemorrhaging)		Suber et al. 1989
			Hemato	51 F	321 F (decreased white blood cells, and lymphocytes in females)		
				51 M	321 M (decreased sorbitol dehydrogenase, gamma glutamyl transferase)		
			Hepatic	707			
			Renal	51	321 (decreased kidney weight)		
			Bd Wt	51 F	321 F (decreased body weight)		
Immunological/Lymphoreticular							
2	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d		707			Suber et al. 1989
CHRONIC EXPOSURE							
Systemic							
3	Monkey (Macacus Rhesus)	13 mo continuous	Resp	112			Robertson et al. 1947
			Gastro	112			
			Hemato		112 (increased hemoglobin)		
			Hepatic	112			
			Renal	112			
			Endocr	112			
			Bd Wt	112			

TABLE 2-2. Levels of Significant Exposure to Propylene Glycol - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
4	Rat (NS)	18 mo continuous	Resp	112			Robertson et al. 1947
			Hepatic	112			
			Renal	112			
			Bd Wt		112M (50% increase in body weight)		
	Immunological/Lymphoreticular						
5	Monkey (Macacus Rhesus)	13 mo continuous		112			Robertson et al. 1947
6	Rat (NS)	18 mo continuous		112			Robertson et al. 1947
	Reproductive						
7	Rat (NS)	18 mo continuous		112			Robertson et al. 1947

[a]The number corresponds to entries in Figure 2-2.

[b]Used to derive an intermediate inhalation minimal risk level (MRL) of 0.009 ppm; LOAEL divided by an uncertainty factor of 1,000 (10 for extrapolation from animals to humans,10 for use of a LOAEL, and 10 for human variability) and multiplied by 6/24 and 5/7 to adjust for intermittent exposure of 6 hours/day, 5 days/week.

Bd Wt = body weight; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; M = male; mo = month(s); NOAEL = no-observable-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s)

Figure 2-2. Levels of Significant Exposure to Propylene Glycol - Inhalation

Intermediate (15-364 days)

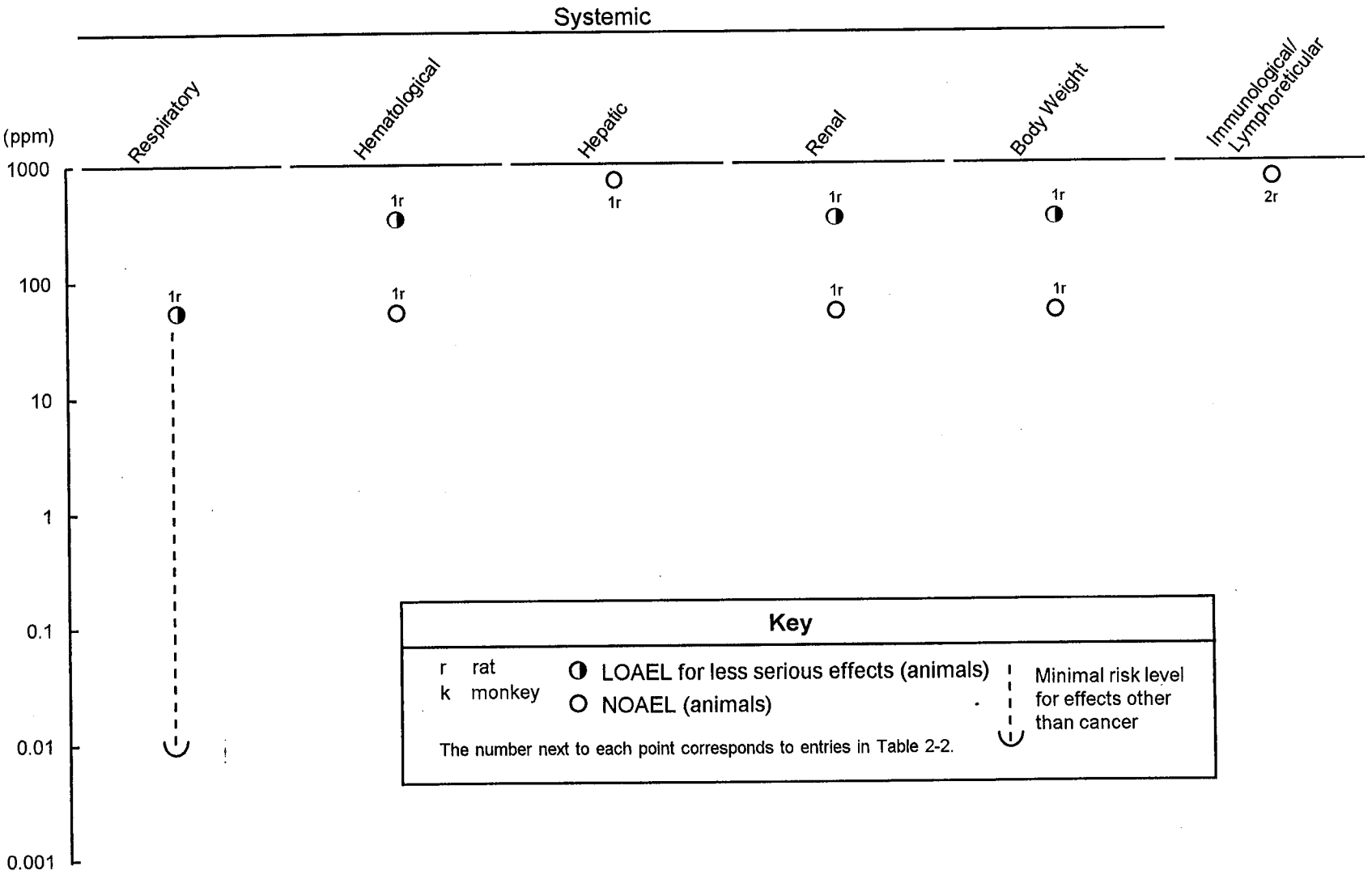
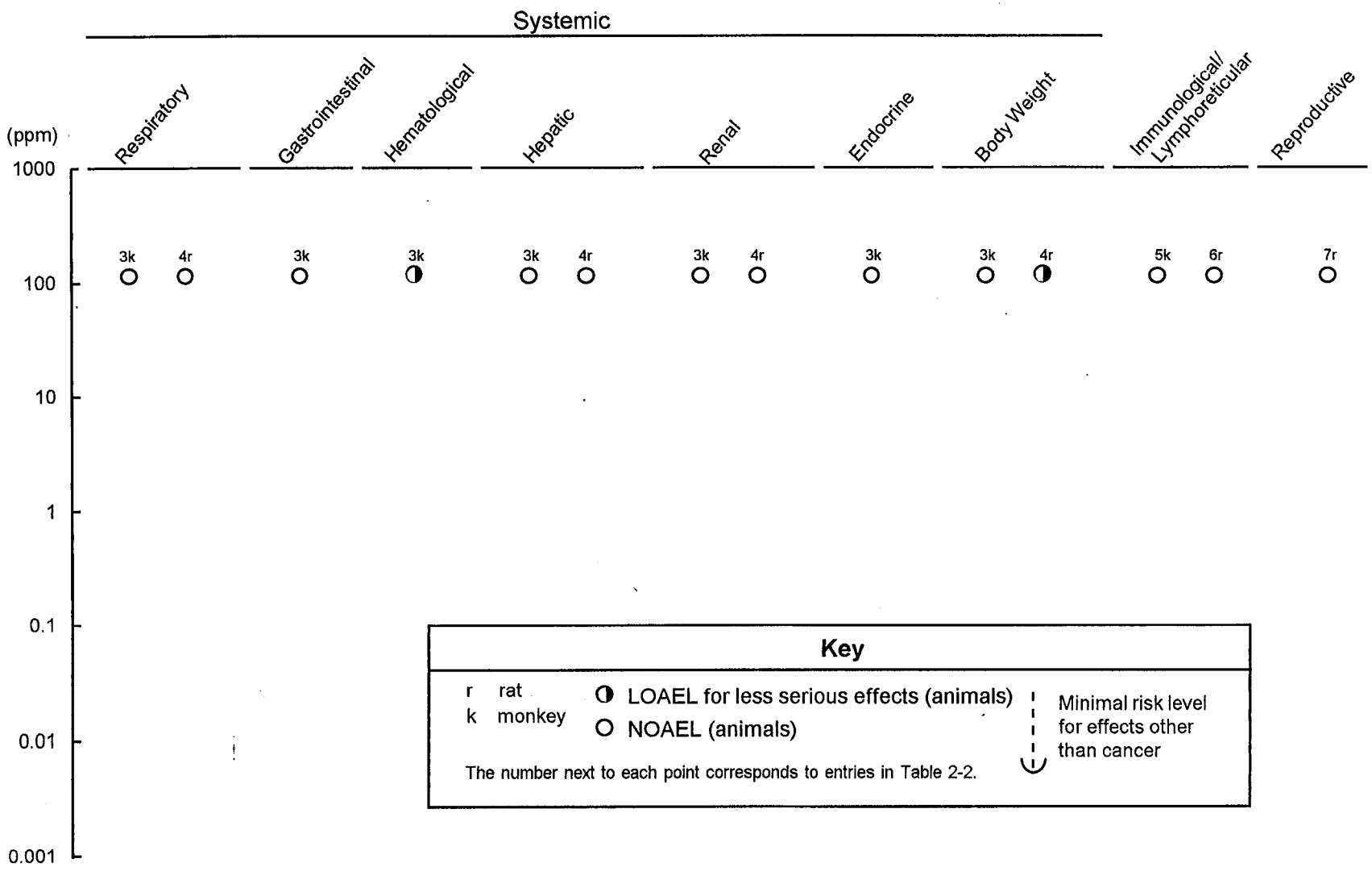


Figure 2-2. Levels of Significant Exposure to Propylene Glycol - Inhalation (continued)

Chronic (≥365 days)



exposure to concentrations of propylene glycol up to 112 ppm for 13-18 months caused no adverse effects on the respiratory system (Robertson et al. 1947). These studies do not indicate a basis for concern because comparable exposure conditions do not occur for the general population.

Gastrointestinal Effects. In rhesus monkeys and rats, continuous exposure to air concentrations of propylene glycol up to 112 ppm for 13-18 months caused no adverse effects on the gastrointestinal system (Robertson et al. 1947).

Hematological Effects. After inhalation exposure to mean daily concentrations of 7-19 ppm ethylene glycol for 20-22 hours per day for 4 weeks, a group of 20 volunteers showed no significant alterations of hematologic parameters, including hematocrit, hemoglobin, and differential counts (Wills et al. 1974). The authors speculate that an insufficient amount of vaporized ethylene glycol was absorbed through the epithelium of the respiratory tract to cause toxicity, although total absorption of inhaled aerosols would be expected.

Limited information was available on hematological effects of propylene glycol. The results from animal studies indicate that intermediate and chronic exposure to propylene glycol may lead to hemolysis of red blood cells (RBC). After intermediate inhalation exposure to 321 ppm propylene glycol, female rats had decreased white blood cell (WBC) counts, while exposure to 707 ppm of propylene glycol caused decreased mean corpuscular hemoglobin concentrations and white blood cell counts; no dose-related changes in RBCs were observed in male rats under the same regimen (Suber et al. 1989). In rhesus monkeys, continuous exposure to concentrations of propylene glycol in air up to 112 ppm for 13 months caused increased hemoglobin counts compared to the control animals (Robertson et al. 1947). These results indicate that there may, be species differences with regard to the effect of propylene glycol on red blood cells.

Hepatic Effects. Rats exposed to 1,000 ppm ethylene glycol on gestational day (Gd) 6-15 by whole body inhalation procedures exhibited increased absolute and relative liver weight; whereas mice. exposed to 827 ppm ethylene glycol under the same regimen showed no hepatic effects (Tyl 1985, 1988a).

The results from animal studies show that there are no adverse hepatic effects in rats after intermediate inhalation exposure to 707 ppm of propylene glycol (Suber et al. 1989). In rhesus monkeys and rats,

continuous exposure to air concentrations of propylene glycol up to 112 ppm for 13-18 months caused no adverse effects on the hepatic system (Robertson et al. 1947). Based on these findings, it can be assumed that chronic exposures to moderately high levels of propylene glycol will not have adverse hepatic effects in humans. It is not clear if hepatotoxicity would result after an acute exposure to a high level of propylene glycol. Since levels of propylene glycol in the vicinity of a hazardous waste site would probably be low, it is unlikely that propylene glycol would induce adverse hepatic effects in people living in the area.

Renal Effects. After inhalation exposure to mean daily concentrations of 7-19 ppm ethylene glycol for 20-22 hours per day for 4 weeks, a group of 20 volunteers showed no significant alterations of renal parameters (Wills et al. 1974).

Mice exposed to aerosolized ethylene glycol by nose-only procedures on Gd 6-15 exhibited a decrease in absolute kidney weight at 394 ppm, although no treatment-related microscopic lesions were observed (Tyl 1988a).

Intermediate inhalation exposure of rats to 707 ppm propylene glycol did not cause adverse renal effects (Suber et al. 1989), although kidney weight was reduced at 321 ppm in males and females. In rhesus monkeys and rats, continuous exposure to concentrations of propylene glycoi up to 112 ppm for 13-18 months caused no adverse effects on the renal system (Robertson et al. 1947). These results indicate that exposure to low levels of propylene glycol that may be present at hazardous waste sites is not likely to cause adverse renal effects in the human population living in the vicinity.

Endocrine Effects. In rhesus monkeys and rats, continuous exposure to concentrations of propylene glycol up to 112 ppm for 13-l 8 months caused no adverse effects on the endocrine system (Robertson et al. 1947).

Body Weight Effects. Body weight does not appear to be a sensitive indicator of ethylene glycol toxicity. Only one of the studies in animals which identify systemic effects shows adverse effects on body weight. Pregnant CD-l mice showed a decrease in body weight and body weight gain after whole body inhalation exposure to 400 ppm ethylene glycol on Gd 6-15, but nose-only exposure to doses up to 985 ppm produced no change in body weight or body weight gain (Tyl 1988a).

Rhesus monkeys continuously exposed to air concentrations of propylene glycol up to 112 ppm for 13 months exhibited no adverse body weight effects, whereas rats exposed for 18 months under the same conditions exhibited a 50% decrease in body weight (Robertson et al. 1947). Intermediate inhalation exposure of female rats to 321 ppm caused decreased body weight (Suber et al. 1989).

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located specifically regarding adverse immunological effects in humans or animals after inhalation exposure to ethylene glycol. However, after intermediate inhalation exposure of 20 volunteers to 7-19 ppm ethylene glycol, no significant alterations in lymphocyte or monocyte counts were noted (Wills et al. 1974).

Currently, there is no evidence that acute exposure to high concentrations of ethylene glycol adversely affects immunological functions. Intermediate exposure to low concentrations of ethylene glycol that may be present in the vicinity of hazardous waste sites is not likely to produce adverse immunological effects in populations residing in the area.

No studies were located specifically regarding adverse immunological effects in humans or animals after inhalation exposure to propylene glycol.

Twenty-nine monkeys were continuously exposed to propylene glycol vapor over a period of 13 months, at doses of 32-112 ppm (Robertson et al. 1947). There was no effect on the spleen. Similarly, rats exposed to 55-l 12 ppm propylene glycol vapor continuously for 18 months showed no effect on the spleen (Robertson et al. 1947). Young, healthy adult Sprague-Dawley rats divided into 4 groups of 19 males and 19 females each. Three groups were exposed for 5 days per week, 6 hours per day for 13 weeks by nose-only inhalation to mean target aerosol concentrations of 5 1, 321, or 707 ppm propylene glycol, respectively (Suber et al. 1989). The fourth group (control group) was exposed to humidified, filtered room air. There was no effect on spleen weight. -’

The highest NOAEL values and all reliable LOAEL values for immunological and lymphoreticular effects in each species and duration category for propylene glycol after inhalation exposure are reported in Table 2-2 and plotted in Figure 2-2.

2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in animals after inhalation exposure to ethylene glycol. Little information was available on neurological effects of inhaled ethylene glycol in humans. A group of 22 volunteers, exposed for 20-22 hours per day for 4 weeks. to an average concentration of 7-19 ppm aerosolized ethylene glycol, exhibited only slight headache and backache as a result (Wills et al. 1974). No effects were seen in a battery of psychological tests conducted on these subjects (Wills et al. 1974).

No studies were located regarding neurological effects in humans or animals after inhalation exposure to propylene glycol.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category for ethylene glycol after inhalation exposure are reported in Table 2-1, and plotted in Figure 2- 1.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to ethylene glycol.

Whole body exposure of pregnant CD-l mice to 60-1,000 ppm aerosolized ethylene glycol for 6 hours a day on Gd 6-15 caused a decrease in the number of live implants at 400 ppm, but no effect on reproductive parameters was observed in CD rats dosed under the same regimen (Tyl 1985). The study was limited by the possible confoundin,0 factor of ingestion of ethylene glycol from the fur of exposed animals (in grooming). In a companion study, nose-only exposure of CD-l mice to 197-985 ppm aerosolized ethylene glycol using the same study design resulted in no postimplantation loss (Tyl 1988a). An additional study in CD-l mice, using nose-only procedures and the same exposure regimen, showed increased postimplantation loss at 827 ppm (Tyl 1988a).

No studies were located regarding reproductive effects in humans after inhalation exposure to propylene glycol.

White rats exposed continuously to a concentration of 55-112 ppm propylene glycol for 18 months showed no adverse effects on the ability to produce live young, or on survival of the offspring (Robertson et al. 1947).

The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category for ethylene glycol after inhalation exposure are reported in Table 2-l and plotted in Figure 2-l. The NOAEL value for reproductive effects in rats for the chronic-duration category for propylene glycol after inhalation exposure is reported in Table 2-2 and plotted in Figure 2-2.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to ethylene glycol.

Whole body exposure of pregnant CD-l mice to 60-1,000 ppm aerosolized ethylene glycol for 6 hours a day on Gd 6-15 caused a decrease in the number of live implants and in the weight of live fetuses, and an increase in the incidence of external, visceral, and skeletal malformations (Tyl 1985). The study was limited by the possible confounding factor of ingestion of ethylene glycol from the fur of exposed animals (in grooming). In a companion study, nose-only exposure to 197-985 ppm aerosolized ethylene glycol using the same study design resulted in reduced live fetal body weight at 985 ppm, but no increase in malformation incidence at any dose (Tyl 1988a). An additional study in CD-l mice, using nose-only procedures and the same exposure regimen, showed reduced fetal body weight at 827 ppm (Tyl 1988a). Similar studies conducted in Sprague-Dawley rats revealed reduced ossification at some sites in the axial skeleton after whole body exposure to 400 ppm aerosolized ethylene glycol (Tyl 1985).

No studies were located regarding developmental effects in humans or animals after inhalation exposure to propylene glycol.

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category for ethylene glycol after inhalation exposure are reported in Table 2-l and plotted in Figure 2-l.

2.2.1.7 Genotoxic Effects

No studies were located regarding in viva genotoxic effects in humans or animals after inhalation exposure to ethylene glycol or propylene glycol.

Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

One epidemiologic study on renal cancer mortality examined the work and health histories of 1,666 employees of a chemical plant and found no elevation in the odds ratio for workers exposed to ethylene glycol (Bond et al. 1985), although the sample size was quite small. Exposure was presumed to be by inhalation.

No studies were located regarding cancer effects in animals after inhalation exposure to ethylene glycol.

Because of information available, it is reasonable to conclude that inhalation exposures to ethylene glycol incurred from waste site sources pose negligible risks of cancer.

No studies were located regarding cancer effects in humans or animals after inhalation exposure to propylene glycol.

2.2.2 Oral Exposure

Ethylene glycol is a colorless, water-soluble liquid with a sweet taste and little or no odor, most commonly used as an antifreeze fluid. The ready availability of antifreeze mixtures makes ethylene glycol intoxication a significant medical and veterinary problem. Antifreeze mixtures c+t.in up to 95% ethylene glycol (Mallya et al. 1986; Siew et al. 1975a). The exposure route most commonly associated with adverse effects is oral ingestion.

Propylene glycol is also a clear, practically odorless and tasteless liquid that is slightly syrupy at room temperature. Oral exposure to propylene glycol occurs through ingestion of foods, since propylene

glycol is approved for use as a food additive. Ingestion by humans is not frequently associated with adverse effects.

2.2.2.1 Death

The American Association of Poison Control Centers reported nine and five fatalities for 1989 and 1990, respectively, due to ethylene glycol ingestion (Litovitz et al. 1990, 1991). Several other fatal ethylene glycol poisonings have been reported in earlier studies. Seven case reports of deaths in humans resulting from accidental or intentional ingestion of ethylene glycol or antifreeze containing 99% ethylene glycol have been located (Godolphin et al. 1980; Gordon and Hunter 1982; Hewlett et al. 1986; Jacobsen et al. 1984; Siew et al. 1975a; Zeiss et al. 1989). In one case, the dose of ingested ethylene glycol was known, 4,071 mg/kg (Siew et al. 1975a). The 22-year-old male who ingested 300 mL of antifreeze lapsed into a coma 24 hours after hospital admission and died 24 hours later. A dose of 7,850 mg/kg can be estimated in the case of a 73-year-old male who consumed 500 mL of 95% ethylene glycol and died of myocardial failure after 68 hours (Gordon and Hunter 1982). Two deaths involved an 18-year-old male who died of brain stem failure (Godolphin et al. 1980) and a 29-year-old male who died of renal failure (Zeiss et al. 1989). The accidental death of a 53-year-old female patient occurred following dialysis with a solution accidentally prepared with ethylene glycolcontaminated water (Anonymous 1987). After developing metabolic acidosis, the patient lapsed into irreversible shock and coma, and died 24 hours after'dialysis. Twelve other fatal cases of accidental or intentional poisoning have been reported in similar epidemic-like occurrences (Karlson-Stilber and Persson 1992; Walton 1978). The amount of ingested ethylene glycol ranged from 150 to 1,500 mL (2,379-23,786 mg/kg), except for 7 cases in which the amount was not known.

Male Wistar rats with intact livers were given 12,900 mg/kg ethylene glycol in a single oral dose, and had a 55% mortality rate within 48 hours (Richardson 1973). In the same study, partially hepatectomized male Wistar rats with l/3 and 2/3 hepatectomies had 27% and 13% mortality, respectively, indicating decreased metabolism of ethylene glycol, decreased production of toxic metabolite, and subsequent death (Richardson 1973). Female Fischer 344 rats exhibited an oral LD_{50} of 4,000 mg/kg (Clark et al. 1979). Pregnant CD-l mice given 11,090 mg/kg/day ethylene glycol orally on gestational days (Gd) 7-14 showed 10% mortality (Schuler et al. 1984), whereas pregnant rabbits exhibited 42% mortality after receiving 2,000 mg/kg/day ethylene glycol orally on Gd 6-19 (Tyl et al. 1993). Male Fischer 344/N rats fed 2,500 mg/kg/day ethylene glycol had 40% mortality

after 13 weeks, whereas similarly treated females did not die (Melnick 1984). Male Sprague-Dawley rats given 500 or 2,000 mg/kg/day ethylene glycol in the feed during a 2-year study showed 100% mortality in each group after 18 months (Blood 1965). Female rats in the same study exhibited 100% mortality only in the 2,000 mg/kg/day group (Blood 1965). Similarly, male Fischer 344 rats given 1,000 mg/kg/day ethylene glycol in the feed all died within 16 months (DePass et al. 1986a; Woodside 1982). Similar findings occurred in cats that were administered ethylene glycol at 4,440 mg/kg orally. All animals developed loss of reflexes, convulsions, central nervous system depression (symptoms not specified), and coma. All animals died 20-36 hours after exposure unless treated with ethanol (Penumarthy and Oehme 1975). Ethylene glycol induced a similar, lethal toxicity in dogs given 4,880 mg/kg orally (Beckett and Shields 1971), whereas in another study, 17-100% of the dogs died within 72 hours after receiving a single oral dose of 4,180-12,540 mg/kg/day ethylene glycol (Kersting and Nielson 1965).

The oral dose of ethylene glycol required to cause death in humans is not well defined in the literature. However, the minimum lethal dose for adults is thought to be 1.4 mL/kg of 95% ethylene glycol, or about 1,330 mg ethylene glycovkg body weight (Parry and Wallach 1974; Robinson and McCoy 1989; Siew et al. 1975a).

The possibility exists for humans to accidentally ingest sufficient amounts of ethylene glycol in antifreeze to cause irreversible adverse effects or death. However, it is very unlikely that persons living in the vicinity of hazardous waste sites could ingest sufficient amounts of soil or water contaminated with ethylene glycol to cause death.

No studies were located regarding death in humans after oral exposure to propylene glycol.

Oral LD_{50} values have been reported in rats (range, 8-46 g/kg), mice (range, 25-32 g/kg), and guinea pigs (range, 18-20 g/kg) after acute oral exposure to propylene glycol (Clark et al. 1979; EPA 1987a; Ruddick 1972). Male Wistar rats (6/group) were orally dosed with saline or 2,942 mg/kg/day , propylene glycol in water for 10, 20, or 30 days (Morshed et al. 1991a). No death was observed. A fatal case of propylene glycol poisoning occurred in a horse given 3.8 L (7,904 mg/kg) of propylene glycol instead of mineral oil. The horse died of respiratory arrest 28 hours after administration (Dorman and Haschek 1991). It is unlikely that sufficient amounts of propylene glycol can be present or ingested near hazardous waste sites to cause death among people living in the area.

All reliable LOAEL and LD_{50} values for death in each species and duration category for ethylene glycol after oral exposure are reported in Table 2-3, and plotted in Figure 2-3. The LD_{50} value for death in rats after acute duration oral exposure to propylene glycol are reported in Table 2-4 and plotted in Figure 2-4.

2.2.2.2 Systemic Effects

No studies were located regarding hematological, musculoskeletal, endocrine, hepatic, dermal, ocular, or body weight effects in humans, or ocular effects in animals after oral exposure to ethylene glycol. No studies were located regarding respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, or body weight effects in humans, or musculoskeletal, dermal, or ocular effects in animals after oral exposure to propylene glycol.

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category for ethylene glycol after oral exposure are reported in Table 2-3 and Figure 2-3. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category for propylene glycol after oral exposure are reported in Table 2-4 and Figure 2-4.

Respiratory Effects. Respiratory system involvement occurs 12-24 hours after ingestion of sufficient amounts of ethylene glycol and is considered to be a second stage in ethylene glycol poisoning (Vale 1979). The symptoms include hyperventilation (Godolphin et al. 1980; Gordon and Hunter 1982), shallow rapid breathing (Woolf et al. 1992; Zeiss et al. 1989), and generalized pulmonary edema with calcium oxalate crystals occasionally present in the lung parenchyma (Vale 1979). Respiratory failure was observed in a woman who had consumed 9,771 mg/kg ethylene glycol (as antifreeze) (Blakeley et al. 1993). It appears that respiratory system involvement is dose-dependent and occurs concomitantly with cardiovascular changes. Symptoms related to acidosis such as hyperpnea and tachypnea are frequently observed; however, major respiratory morbidities such as pulmonary edema rarely occur, having been reported in only 5 of 36 severely poisoned cases (Karlson-Stilber and Persson 1992).

Respiratory effects have been observed in dogs after oral exposure to ethylene glycol (Kersting and Nielson 1965). Congestion, edema, hyperpnea, and tachypnea were observed in dogs during the second or third hour after a single oral dose of up to 12,540 mg/kg. The doses at which the

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	ACUTE EXPOSURE						
	Death						
1	Human	once				7070 M (death 68 hours after ingestion of EG)	Gordon and Hunter 1982
2	Human	once				4071 M (death 48 hrs after ingestion)	Siew et al. 1975a
3	Human	once				2379 (death in 6/11)	Walton 1978
4	Rat (Fischer 344)	once (G)				4000 F (LD_{50})	Clark et al. 1979
5	Mouse (Swiss CD-1)	8 d Gd 7-14 1x/d (G)				11090 F (5/50 died)	Schuler et al. 1984
6	Rabbit (New Zealand)	14 d Gd 6-19 1x/d (GW)				2000 F (8/19 died)	Tyl et al. 1993
	Systemic						
7	Human	once	Metab			4332 M (severe metabolic acidosis)	Cheng et al. 1987
8	Human	once	Resp		7070 M (hyperventilation)		Gordon and Hunter 1982
			Cardio			7070 M (myocardial failure)	
			Renal			7070 M (renal failure)	
			Metab			7070 M (metabolic acidosis)	

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
9	Human	once	Renal			11238 F (calcium oxalate crystalluria)	Heckerling 1987
			Metab			11238 F (metabolic acidosis, increased bromide; ion gap)	
10	Human	once	Renal			2714 M (renal failure)	Mallya et al. 1986
11	Human	once	Cardio			3171 M (tachycardia, ventricular gallop)	Parry and Wallach 1974
			Renal			3171 M (calcium oxalate crystalluria, renal failure)	
			Metab			3171 M (metabolic acidosis)	
12	Human	once	Renal			7600 M (ethylene glycol in urine)	Peterson et al. 1981
			Metab			7600 M (ethylene glycol in blood; metabolic acidosis)	
13	Human	once	Cardio			4071 M (ventricular tachycardia, cardiac arrest)	Siew et al. 1975a
			Renal			4071 M (oxalate nephrosis)	
			Metab			4071 M (metabolic acidosis)	
14	Human	once (W)	Gastro			12839 M (upper gastrointestinal bleeding)	Spillane et al. 1991
			Renal			12839 M (increased creatinine, renal failure)	
			Metab			12839 M (metabolic acidosis, ion gap)	
15	Rat (Sprague-Dawley)	10 d Gd 6-15 1x/d (GW)	Bd Wt		2500 F (treatment period weight gain decreased 27%; gestational weight gain decreased 13%)		Marr et al. 1992

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
16	Rat (Sprague-Dawley)	10 d Gd 6-15 1x/d (GW)	Hepatic	2500 F			Neeper-Bradley 1990
			Renal	1000 F	2500 F (increased absolute and relative kidney weight)		
			Bd Wt	1000 F	2500 F (decreased body weight)		
17	Rat (Sprague-Dawley)	Gd 6-20 1x/d (GW)	Renal	250		1250 (oxalate nephrosis, tubular dilatation and degeneration)	NTP 1988
			Bd Wt	2250			
18	Rat (CD)	10 d 1x/d (GW)	Hepatic	2500 F	5000 F (11% decreased liver weight in dams)		Price et al. 1985
			Body Wt		1250 F (17% decreased body weight)		
19	Mouse (B6C3F1)	4 d (GW)	Resp	1000			Hong et al. 1988
			Cardio	1000			
			Gastro	1000			
			Hemato	400 F	200 M (bone marrow 1000 F hypo-cellularity)		
			Hepatic	1000			
			Renal	1000			
20	Mouse (CD-1)	10 d 1x/d (GW)	Hepatic	750 F	1500 F (reduced liver weight in dams)		Price et al. 1985
			Body Wt	750 F	1500 F (31% reduced weight gain)		

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
21	Mouse (CD-1)	10 d Gd 6-15 1x/d (GW)	Hepatic	1500 F			Tyl 1989
			Renal	1500 F			
			Bd Wt	1500 F			
22	Dog	once (F)	Renal			10743 (renal failure, oxalate nephrosis)	Grauer et al. 1987
23	Rabbit (New Zealand)	14 d Gd 6-19 1x/d (GW)	Hepatic	2000 F			Tyl et al. 1993
			Renal			2000 F (intraluminal oxalate crystals, epithelial necrosis, and tubular dilatation and degeneration of the cortical tubules)	
			Bd Wt	2000 F			
24	Cat	once (G)	Renal			4440 (oxalate nephrosis)	Penumarthy and Oehme 1975
	Neurological						
25	Human	once				9771 F (unresponsive, incontinent, no corneal, gag, or deep-tendon reflexes)	Blakeley et al. 1993
26	Human	once				4332 M (tremors, agitation)	Cheng et al. 1987
27	Human	once			7070M (restlessness, violent behavior)		Gordon and Hunter 1982

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
28	Human	once				11238 F (unresponsive to deep pain, delayed pupillary light reflex, no deep tendon or corneal reflex)	Heckerling 1987
29	Human	once				2714 M (bilateral facial paralysis, hearing loss, absent gag reflex, unilateral facial numbness)	Mallya et al. 1986
30	Human	once				3171 M (ataxia, somnolence, slurred speech, stupor, seizures, bilateral 6th nerve paralysis, lethargy)	Parry and Wallach 1974
31	Human	once				4071 (stupor, loss of consciousness, coma)	Siew et al. 1975a
32	Human	once				12839 M (unresponsive, depressed mental status, dysfunction of cranial nerves 9 and 10)	Spillane et al. 1991
33	Dog	once (F)				10743 (depression, ataxia)	Grauer et al. 1987
34	Cat	once (G)				4440 (convulsions and coma)	Penumarthy and Oehme 1975
	Reproductive						
35	Rat (Fischer 344)	10 d Gd 6-15 (F)		1000 F			Maronpot et al. 1983

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
36	Rat (Sprague-Dawley)	10 d Gd 6-15 1x/d (GW)		2500			Neeper-Bradley 1990
37	Rat (Sprague-Dawley)	Gd 6-20 1x/d (GW)		1250		2250 (decreased prenatal viability)	NTP 1988
38	Rat (CD)	10 d Gd 6-15 1x/d (GW)		2500		5000 F (postimplantation loss)	Price et al. 1985
39	Mouse (CD-1)	10 d Gd 6-15 1x/d (GW)				750 F (reduced litter size)	Price et al. 1985
40	Mouse (CD-1)	10 d Gd 6-15 1x/d (GW)		1500			Tyl 1989
41	Rabbit (New Zealand)	14 d Gd 6-19 1x/d (GW)		1000 F		2000 F (abortion or early delivery)	Tyl et al. 1993
	Developmental						
42	Rat (Fischer 344)	10 d Gd 6-15 (F)		1000 F			Maronpot et al. 1983

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
43	Rat (Sprague-Dawley)	10 d Gd 6-15 1x/d (GW)		500		1000 (increased skeletal malformations)	Neeper-Bradley 1990
44	Rat (Sprague-Dawley)	Gd 6-20 1x/d (GW)		1250		2250 (decreased prenatal and postnatal viability, increased malformations in the axial skeleton)	NTP 1988
45	Rat (CD)	10 d Gd 6-15 1x/d (GW)				1250 F (increased skeletal malformations in fetuses)	Price et al. 1985
46	Mouse (Swiss Crl:CD-1)	7 d Gd 8-14 1x/d (GW)		700	2500 (decreased pup body weight on ppd 1 and 4)		Harris et al. 1992
47	Mouse (CD-1)	10 d Gd 6-15 1x/d (GW)				750 F (increased skeletal malformations in fetuses)	Price et al. 1985
48	Mouse (CD-1)	10 d Gd 6-15 1x/d (GW)		150[b]		500 (increased total malformations and one skeletal variation: bilateral extra rib 14)	Tyl 1989
49	Rabbit (New Zealand)	14 d Gd 6-19 1x/d (GW)		2000 F			Tyl et al. 1993

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	INTERMEDIATE EXPOSURE						
	Death						
50	Rat (Fischer 344/N)	13 wk (F)				2500 M (death in 4/10 males)	Melnick 1984
	Systemic						
51	Rat (Fischer 344)	3 gen (F)	Renal	200	1000 (mild focal interstitial nephritis)		DePass et al. 1986b
			Bd Wt	1000			
52	Rat (Fischer 344/N)	13 wk (F)	Renal	625		1250 (oxalate nephrosis, renal failure)	Melnick 1984
			Bd Wt	625 M 2500 F	1250 M (10% decrease in body weight)		
53	Mouse (Swiss Crl:CD-1)	17 d 1x/d (GW)	Hepatic	2500 M			Harris et al. 1992
			Renal	2500 M			
			Bd Wt	2500 M			
54	Mouse (Swiss Crl:CD-1)	20 d 1x/d (GW)	Other	2500 F			Harris et al. 1992

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
55	Mouse (B6C3F1)	13 wk (F)	Hemato	6500			Melnick 1984
			Hepatic	1625 M 6500 F	3250 M (hyaline degeneration of centrilobular hepatocytes)		
			Renal	1625 M 6500 F	3250 M (mild nephrosis and regenerative hyperplasia)		
56	Mouse (JCL-ICR)	5 wk 5d/wk 1x/d (G)	Hemato	4000 M			Nagano et al. 1984
57	Mouse (B6C3F1)	13 wk 1x/d (F)	Hemato	6500			NTP 1992
			Hepatic	1625 M 6500 F	3250 M (hyaline degeneration of centrilobular hepatocytes)		
			Renal	1625	3250 (tubular dilation, vacuolation, degenerative hyperplasia)		
			Bd Wt	819 M 6500 F	1625 M (significantly lower body weight in males)		
	Neurological						
58	Rat (Fischer 344\N)	13 wk (F)		1250 M 2500 F		2500 M (calcium oxalate deposits in brain blood vessel walls)	Melnick 1984

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference
	Reproductive							
59	Rat (Fischer 344)	3 gen (F)		1000				DePass et al. 1986b
60	Mouse (Swiss Crl:CD-1)	17 d 1x/d (GW)		2500				Harris et al. 1992
61	Mouse (Swiss Crl:CD-1)	20 d 1x/d (GW)		700		2500	(decreased live fetuses, increased dead implants, 2/6 litters totally resorbed)	Harris et al. 1992
62	Mouse (JCL-ICR)	5 wk 5d/wk 1x/d (G)		4000M				Nagano et al. 1984
	CHRONIC EXPOSURE							
	Death							
63	Rat (Sprague-Dawley)	2 yr (F)				500 M	(16/16 died within 18 months)	Blood 1965
						2000 F	(16/16 died within 18 months)	
64	Rat (Fischer 344)	24 mo (F)				1000 M	(130/130 males died prior to month 16)	DePass et al. 1986a; Woodside et al. 1982

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Systemic						
65	Rat (Fischer 344)	12 mo (F)	Resp	1000			DePass et al. 1986a; Woodside et al. 1982
			Gastro	1000			
			Hemato	200 M 1000 F	1000 M (decreased hematocrit, reduced RBC, reduced HGB, increased neutrophils)		
			Hepatic	200 F 1000 M	1000 F (fatty metamorphosis)		
			Renal	200 [c] M		1000 M (oxalate nephrosis in males; chronic nephritis)	
				200 F	1000 F (urinary oxalate)		
			Bd Wt	200 M 1000 F	1000 M (weight loss)		
66	Rat (Fischer 344)	24 mo (F)	Resp	200 M 1000 F			DePass et al. 1986a; Woodside et al. 1982
			Gastro	200 M 1000 F			
			Hemato	200 M 1000 F			
			Hepatic	200 M 200 F	1000 F (fatty metamorphosis)		
			Renal	40	200 (urinary oxalate)		

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
67	Mouse (Charles River CD-1)	12 mo (F)	Resp	1000			DePass et al. 1986a
			Cardio	1000			
			Gastro	1000			
			Musc/sk	1000			
			Hepatic	1000			
			Renal	1000			
			Endocr	1000			
			Dermal	1000			
68	Mouse (B6C3F1)	2 yrs 1x/d (F)	Resp	3250 F	6500 F (pulmonary arterial medial hyperplasia)		NTP 1992
			Hepatic	3250 F	6500 F (hyaline degeneration of centrilobular hepatocytes)		
			Bd Wt	6500 F			
69	Mouse (B6C3F1)	2 yr 1x/d (F)	Hepatic	812.5 M	1625 M (hyaline degeneration of centrilobular hepatocytes)		NTP 1992
			Renal	1625 M		3315 M (oxalate nephrosis, urethra oxalate deposits)	
	Immunological/Lymphoreticular						
70	Rat (Fischer)	24 mo contin-uous (F)		200	1000 (M: increased neutrophils; F: hemosiderosis in the lymph nodes)		DePass et al. 1986a; Woodside 1982

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
71	Mouse (Charles River CD-1)	12 mo (F)		1000			DePass et al. 1986a
	Reproductive						
72	Rat (Fischer 344)	24 mo (F)		1000			DePass et al. 1986a; Woodside et al. 1982
73	Mouse (Charles River CD-1)	24 mo (F)		1000			DePass et al. 1986a

[a]The number corresponds to entries in Figure 2-3.

[b]Used to derive an acute oral minimal risk level (MRL) of 2.0 mg/kg/day; NOAEL divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability)

[c]Used to derive a chronic oral MRL of 2.0 mg/kg/day; NOAEL divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability)

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; gen = generation; (GW) = gavage in water; HGB = hemoglobin; Hemato = hematological; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; Metab = metabolic; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; ppd = post-parturition day; RBC = red blood cell; Resp = respiratory; wk = week(s); x = times; yr = year(s)

Figure 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral

Acute (≤14 days)

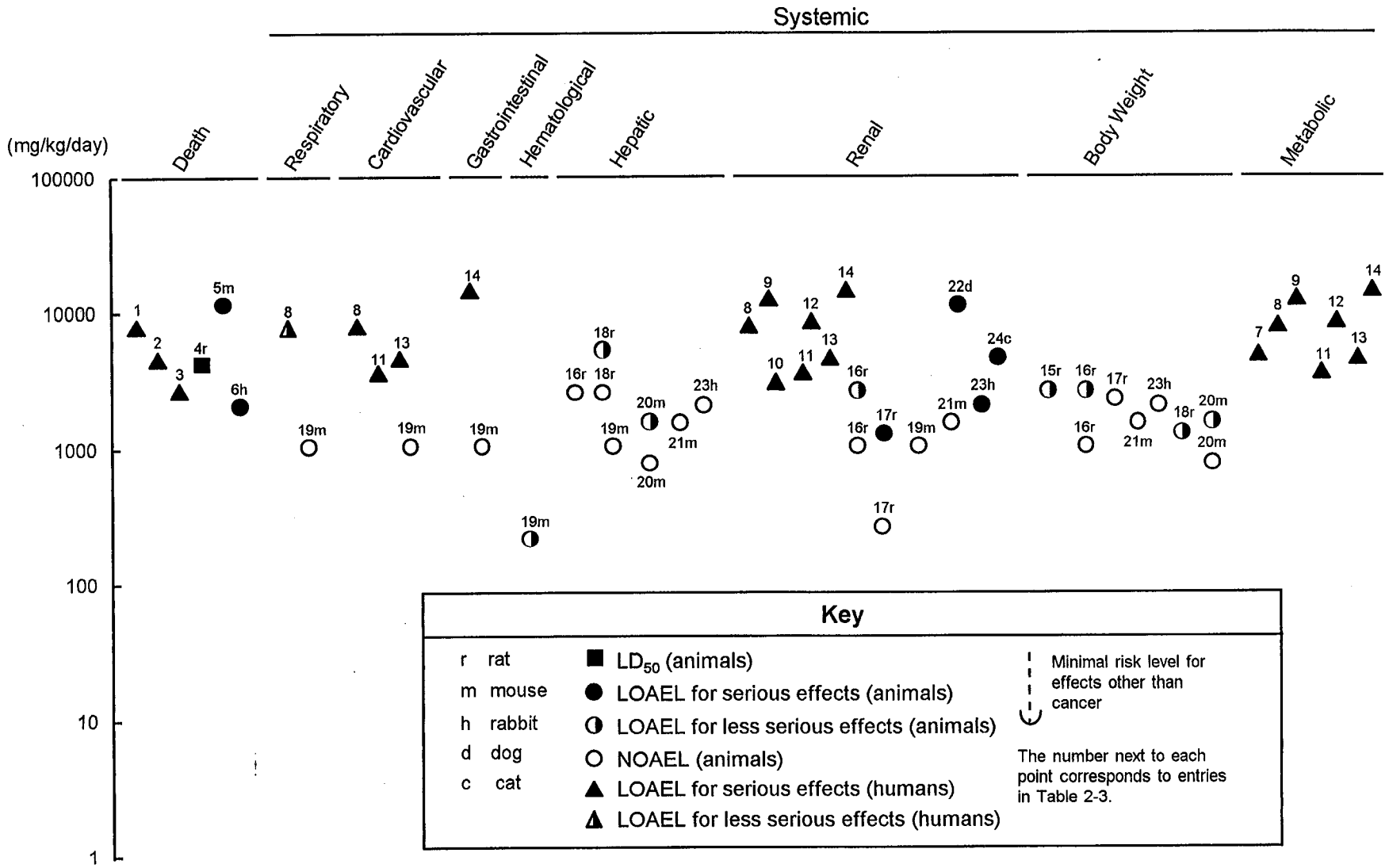


Figure 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Acute (≤14 days)

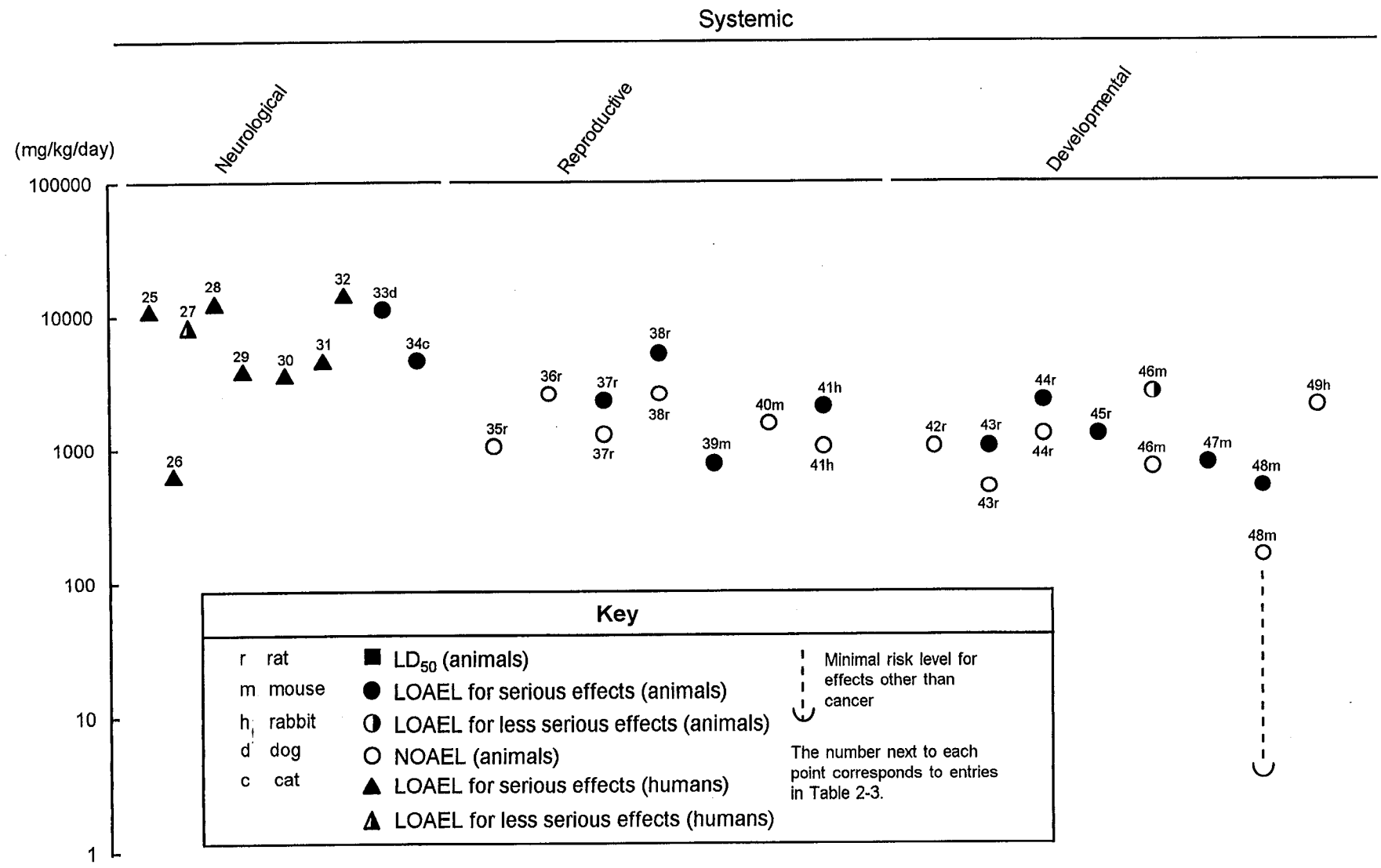


Figure 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Intermediate (15-364 days)

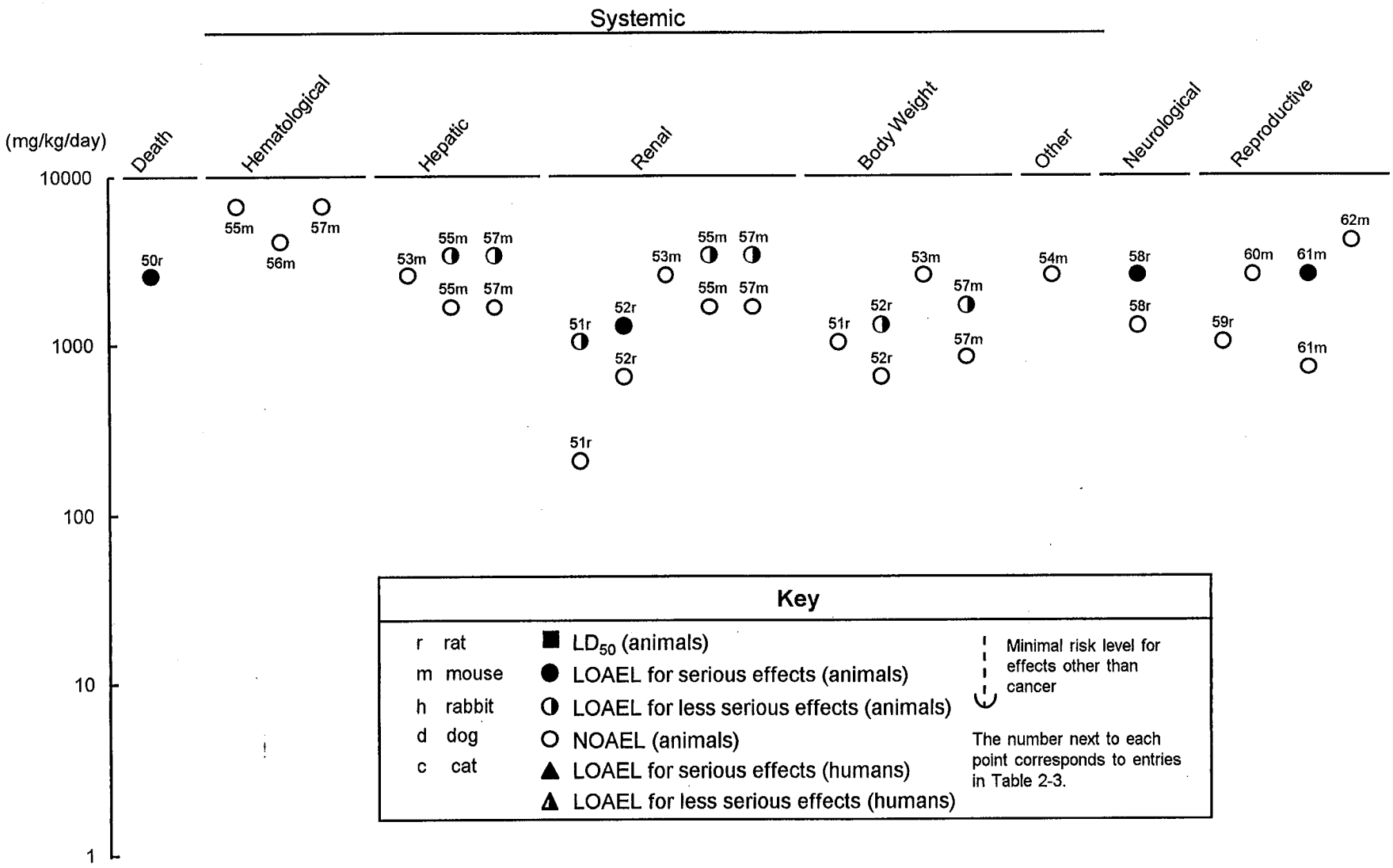


Figure 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Chronic (≥365 days)

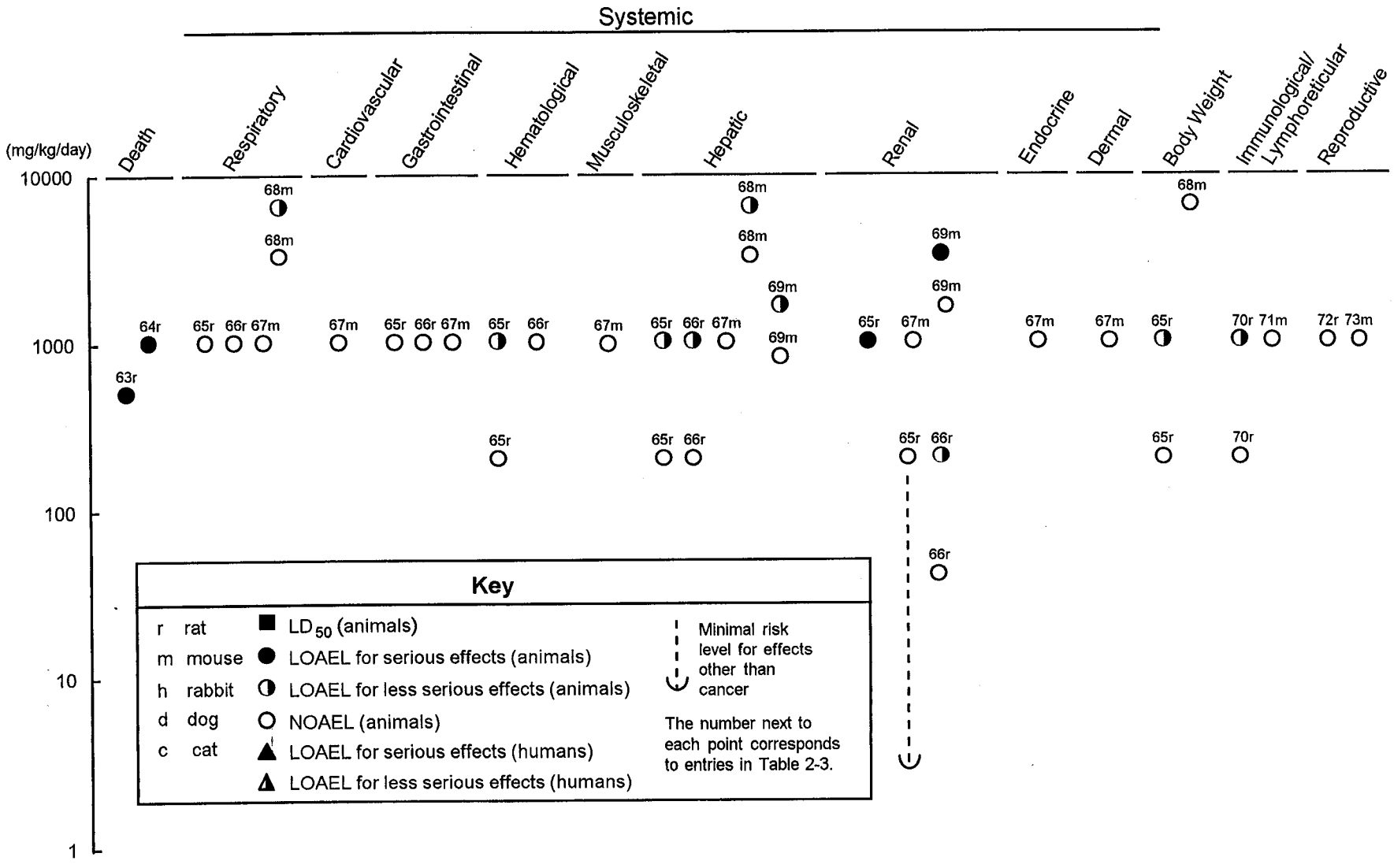


TABLE 2-4. Levels of Significant Exposure to Propylene Glycol - Oral

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	ACUTE EXPOSURE						
	Death						
1	Rat (Fischer 344)	once (G)				22800 F (LD_{50})	Clark et al. 1979
	Systemic						
2	Rat (Fischer 344)	once (G)	Gastro			23500 F (hemorrhagic enteritis)	Clark et al. 1979
			Hemato			23500 F (lymphocyte depletion)	
			Endocr			23500 F (adrenocortical hemorrhage)	
3	Cat (NS)	14 d (F)	Hemato		3600 (reticulocytosis, increased Heinz bodies, increased severe mechanical fragility)		Weiss et al. 1992
	Immunological/Lymphoreticular						
4	Cat (NS)	14 d (F)			3600 (decreased haptoglobin concentrations)		Weiss et al. 1992
	Neurological						
5	Rat (Fischer 344)	once (G)				22800 F (lethargy and coma)	Clark et al. 1979
	Reproductive						
6	Mouse (CD-1)	5 d 1x/d (GW)		10000			Kavlock et al. 1987

TABLE 2-4. Levels of Significant Exposure to Propylene Glycol - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Developmental						
7	Mouse (CD-1)	5 d 1x/d (GW)		10000			Kavlock et al. 1987
	INTERMEDIATE EXPOSURE						
	Systemic						
8	Cat	13 wk (F)	Hemato		1260 (increased Heinz bodies, decreased RBC survival)		Bauer et al. 1991
9	Cat	13 wk (F)	Hemato		2750 (increased Heinz bodies, increased punctate reticulocytes, decreased RBC survival)		Bauer et al. 1992
10	Cat	5 wk (F)	Hemato		1600 (Heinz body formation)		Christopher et al. 1989a
			Renal	1600			
11	Cat	3 wk (F)	Hemato			8000 (hypercellularity)	Christopher et al. 1989a
			Renal		8000 (polyuria, polydipsia)		
12	Cat Mongrel	22-35 d (F)	Renal	1600	8000 (polyuria, polydipsia)		Christopher et al. 1990b
			Metab		1600 (increased anion gap, increased D-lactate)		
13	Cat	17 wk (F)	Hemato		2400 (Heinz body formation)		Weiss et al. 1990

TABLE 2-4. Levels of Significant Exposure to Propylene Glycol - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Neurological						
14	Cat Mongrel	22-35 d (F)		1600		8000 (ataxia, CNS depression, decreased activity)	Christopher et al. 1990b
	Reproductive						
15	Mouse (Swiss CD-1)	15-18 wk daily (W)		10118			NTP 1985
	Developmental						
16	Mouse (Swiss CD-1)	15-18 wk daily (W)		10118			NTP 1985
	CHRONIC EXPOSURE						
	Systemic						
17	Rat	2 yr (F)	Resp	2500			Gaunt et al. 1972
			Cardio	2500			
			Hemato	2500			
			Hepatic	2500			
			Renal	2500			
			Endocr	2500			
18	Dog	2 yr (F)	Hemato	2000	5000 (decreased erythrocytes, hemoglobin, hematocrit)		Weil et al. 1971
			Hepatic	5000			
			Renal	5000			
			Bd Wt	5000			

TABLE 2-4. Levels of Significant Exposure to Propylene Glycol - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	Immunological/Lymphoreticular						
19	Dog	2 yr (F)		5000			Weil et al. 1971

[a]The number corresponds to entries in Figure 2-4.

Bd Wt = body weight; Cardio = cardiovascular; CNS = central nervous sytem; d = day(s); Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; (GW) = gavage in water; Hemato = hematological; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; metab = metabolic; NOAEL = no-observable-adverse-effect level; Resp = respiratory; RBC = red blood cell; (W) = gavage in water; wk = week(s); x = times; yr = year(s)

Figure 2-4. Levels of Significant Exposure to Propylene Glycol - Oral

Acute (≤14 days)

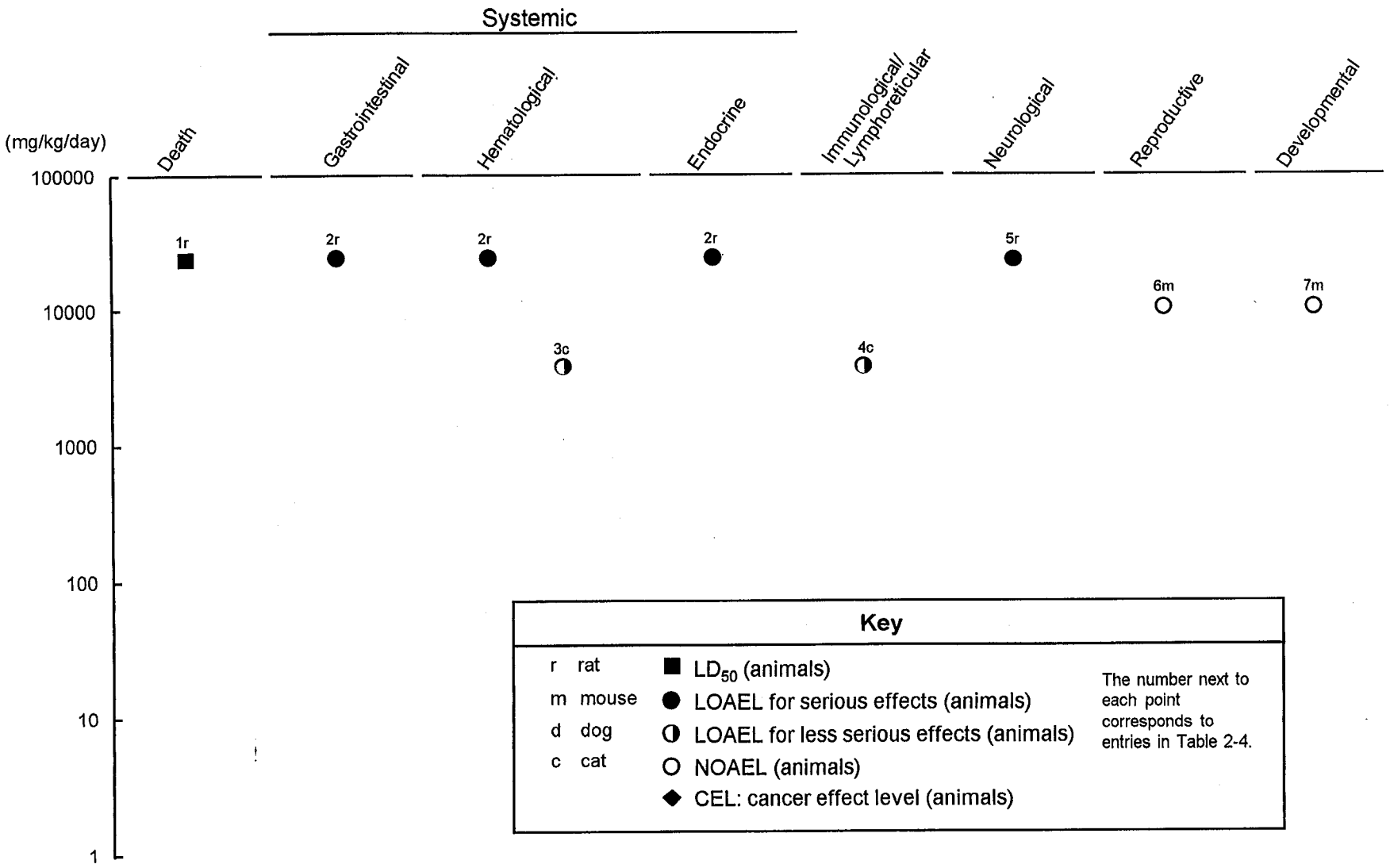


Figure 2-4. Levels of Significant Exposure to Propylene Glycol - Oral (continued)

Intermediate (15-364 days)

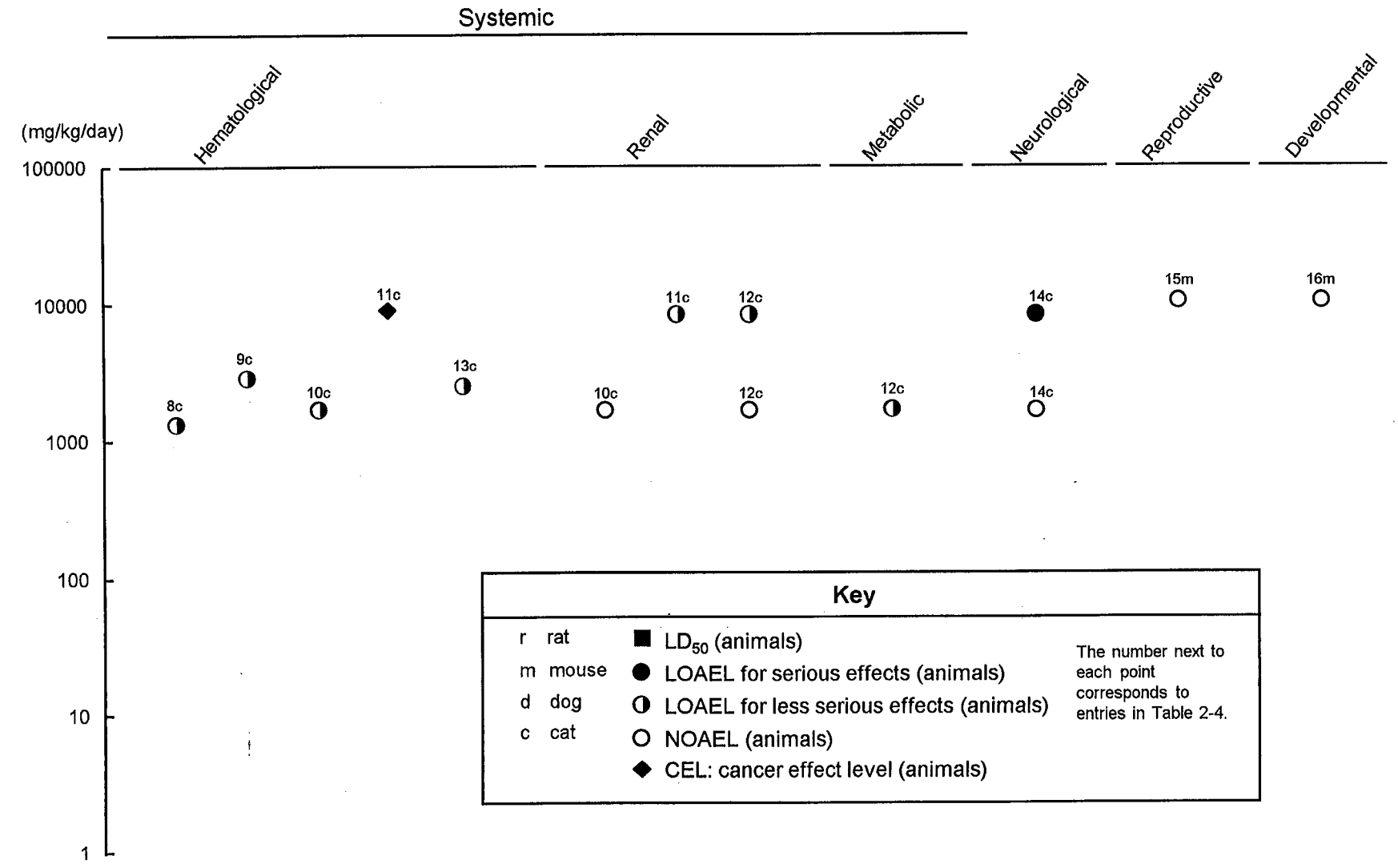
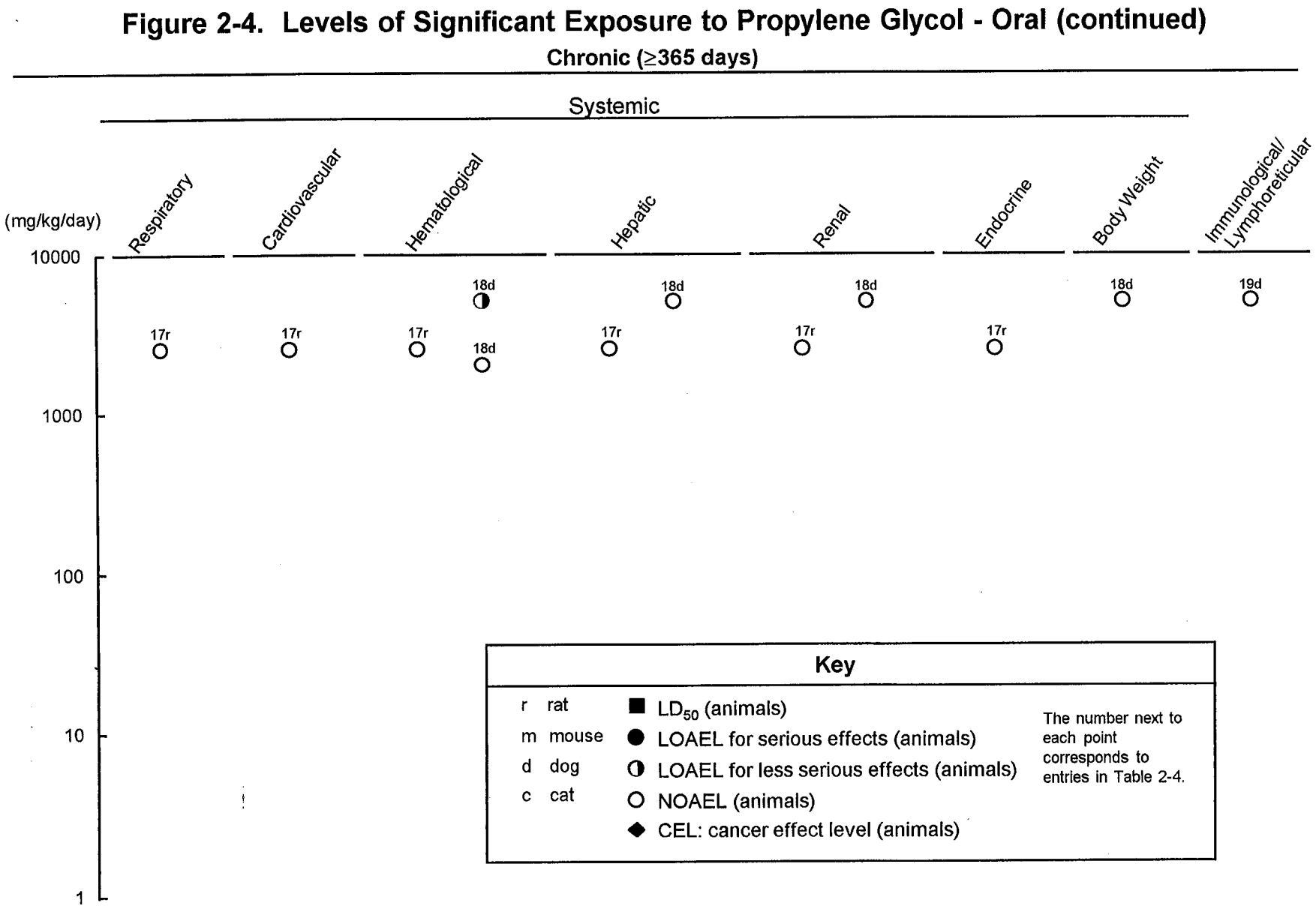


Figure 2-4. Levels of Significant Exposure to Propylene Glycol - Oral (continued)



respiratory effects were seen were not specified. General mineralization of soft tissues, including pulmonary tissue, was noted in male Fischer 344 rats after a l-year exposure to 1,000 mg/kg/day ethylene glycol in the feed (DePass et al. 1986a; Woodside 1982). This effect may be the result of altered calcium metabolism as a result of ethylene glycol exposure (Rajagoopal et al. 1977).

In rats there were no changes in any of the respiratory parameters after 2 years of chronic oral exposure to 2,500 mg/kg/day propylene glycol (Gaunt et al. 1972).

Cardiovascular Effects. Cardiovascular system involvement in humans occurs at the same time as respiratory system involvement, during the second phase of oral ethylene glycol goisoning, which is 12-24 hours after acute exposure (Vale 1979). The symptoms of cardiac involvement include tachycardia, ventricular gallop (Parry and Wallach 1974; Siew et al. 1975a), and cardiac dilatation (Vale 1979). Repeated cardiac arrhythmias were observed prior to cardiac arrest and death in a 22-year-old man who ingested 4,071 mg/kg of ethylene glycol (Siew et al. 1975a). Episodes of hypotension were also observed prior to renal failure and death in a 73-year-old man who ingested 7,850 mg/kg ethylene glycol, contained in antifreeze (Gordon and Hunter 1982). As in the case of respiratory effects, cardiovascular involvement occurs with ingestion of relatively high doses of ethylene glycol. Nevertheless, circulatory disturbances are a rare occurrence, having been reported in only 8 of 36 severely poisoned cases (Karlson-Stilber and Persson 1992). Therefore, it appears that acute exposure to high levels of ethylene glycol can cause serious cardiovascular effects; however, it is unlikely that such levels would be found in water close to hazardous waste sites and consumed by those living in the vicinity. The effects of a long-term, low-dose exposure are unknown.

In dogs, bradycardia and hemorrhages of the myocardium were found in those fatally exposed to an acute oral dose of ethylene glycol (Kersting and Nielson 1965). General mineralization of soft tissues, including cardiac tissue, was noted in male Fischer 344 rats after a l-year exposure to 1,000 mg/kg/day ethylene glycol in the feed (DePass et al. 1986a; Woodside 1982). This effect may be the result of altered calcium metabolism as a result of ethylene glycol exposure (Rajagoopal et al. 1977).

The heart histopathology of rats after a 2-year oral exposure to 2,500 mg/kg/day of propylene glycol revealed no changes (Gaunt et al. 1972). A similar lack of cardiovascular effects was observed in rats by Morris et al. (1942) after a 23-month exposure to 49,500 mg/kg/day propylene glycol in the feed.

A horse developed myocardial edema prior to death caused by accidental oral administration of 7,904 mg/kg propylene glycol (Dorman and Haschek 1991).

It appears that acute exposure to very high levels of propylene glycol may cause adverse cardiovascular effects, but it is unlikely that such exposures could occur as a result of being in the vicinity of hazardous waste sites.

Gastrointestinal Effects. A 33-year-old man who drank a quart of ethylene glycol (12,840 mg/kg) developed upper gastrointestinal tract bleeding secondary to multiple gastric lesions (Spillane et al. 1991). It is not clear whether or not the gastric lesions were a pre-existing condition in this patient.

General mineralization of soft tissues, including stomach tissue, was noted in male Fischer 344 rats after a l-year exposure to 1,000 mg/kg/day ethylene glycol in the feed (DePass et al. 1986a; Woodside 1982). This effect may be the result of altered calcium metabolism as a result of ethylene glycol exposure (Rajagoopal et al. 1977).

Fischer 344 rats exhibited hemorrhagic enteritis after a single oral dose of 23,500 mg/kg propylene glycol (Clark et al. 1979). The effect of orally administered propylene glycol on the brush border membrane from the jejuno-ileum portion of the intestines of rats was investigated *in vivo* (Morshed et al. 1991a). In rats receiving 2,942 mg/kg propylene glycol for 10-30 days, brush border enzymes including sucrase, lactase, and gamma-glutamyl transpeptidase exhibited a tendency toward increased activity. Absorption of D-glucose and calcium was increased after 10 days of treatment, whereas absorption of D-glucose, glycine, L-aspartic acid, L-lysine, and calcium were elevated after 20 or 30 days of treatment. The structural integrity of the jejunal surface was not adversely affected.

Hematological Effects. The hematological parameters-white blood cells, red blood cells, hematocrit, and hemoglobin-were not affected in mice after acute oral ethylene glycol-treatment, but hypocellularity and suppression of colony-forming units were quite evident at a dose of 1,000 mg/kg/day (Hong et al. 1988). Male mice treated orally with doses of ethylene glycol up to 4,000 mg/kg/day for 5 weeks showed no adverse hematological effects (Nagano et al. 1984). Male Fischer 344 rats treated with 1,000 mg/kg/day of ethylene glycol orally for 2 years had a reduced erythrocyte count, reduced hematocrit, and reduced hemoglobin (DePass et al. 1986a; Woodside 1982).

In another study, male and female Sprague-Dawley rats fed ethylene glycol at doses up to 2,000 mg/kg/day for 2 years showed no significant hematologic effects (Blood 1965).

Because of the availability of ethylene glycol, ingestion of high doses can occur and lead to adverse blood chemistry changes. However, such effects are unlikely to occur in populations living near hazardous waste sites since the ethylene glycol concentration necessary to cause such adverse effects is relatively high.

Limited information was available on hematological effects of propylene glycol in humans after oral exposure. A 39-year-old woman who had ingested propylene glycol and ethanol showed no adverse effects on blood chemistry (Lolin et al. 1988).

The results from animal studies indicate that intermediate and chronic exposure to propylene glycol may lead to hemolysis of red blood cells. Increased numbers of Heinz bodies (sign of red blood cell degeneration) were observed in cats exposed orally to 1,200, 1,600, 2,400, and 3,600 mg/kg of propylene glycol for 2, 5, and 17 weeks, respectively (Christopher et al. 1989a; Weiss et al. 1990, 1992). Other studies indicate increased Heinz body formation and decreased RBC survival in kittens and adult cats ingesting 3,000 mg/kg and 1,400 mg/kg/day, respectively (Bauer et al. 1992). These findings are further supported by results obtained in dogs after chronic oral exposure to 5,000 mg/kg/day (Weil et al. 1971). Red blood cell hemolysis was evidenced by decreased hemoglobin and hematocrit levels, and decreased total red blood cell counts. In rats, however, there were no changes in any of the hematological parameters after 2 years of chronic oral exposure to 2,500 mg/kg/day propylene glycol (Gaunt et al. 1972). These results indicate that there may be species differences with regard to the effect of propylene glycol on red blood cells. Fischer 344 rats exhibited lymphocyte depletion after a single oral dose of 23,500 mg/kg propylene glycol (Clark et al. 1979). Hypocellularity of the bone marrow was observed in cats after intermediate oral exposure to 8,000 mg/kg/day of propylene glycol (Christopher et al. 1989a).

Musculoskeletal Effects. CD-l mice fed up to 1,000 mg/kg/day ethylene glycol for 24 months showed no abnormal musculoskeletal effects (DePass et al. 1986a).

Hepatic Effects. In mice exposed to an oral dose of 1,000 mgkg of ethylene glycol, histopathology did not reveal any liver changes 1, 5, or 14 days after treatment (Hong et al. 1988).

Neither was there any effect in male mice after 17 days of oral treatment with 2,500 mg/kg/day (Harris et al. 1992). Similarly, Fischer 344 rats fed up to 2,500 mg/kg/day ethylene glycol for 13 weeks showed no treatment-related effect on the liver (Melnick 1984). Male mice fed doses of ethylene glycol up to 6,500 mg/kg/day for 13 weeks exhibited degeneration of the centrilobular hepatocytes at doses ≥3,250 mg/kg/day (Melnick 1984; NTP 1992). Pregnant female Sprague-Dawley rats exhibited an 11% decrease in liver weight after oral dosing with 5,000 mg/kg/day ethylene glycol on Gd 6-15 (Price et al. 1985). However, pregnant CD rats and CD-l mice dosed with up to 2,500 mg/kg/day or 1,500 mg/kg/day ethylene glycol, respectively, using the same regimen, showed no hepatic effects (Neeper-Bradley 1990; Tyl 1989). Similarly, New Zealand White rabbits showed no hepatic effects after oral exposure to 2,000 mg/kg/day ethylene glycol on Gd 6-19 (Tyl et al. 1993). Fatty change of the liver was seen in female Fischer 344 rats fed 1,000 mg/kg/day of ethylene glycol for 2 years (DePass et al. 1986a; Woodside 1982). Ethylene glycol is absorbed relatively quickly after ingestion and evenly distributed throughout the body, while the liver is the main site of its oxidative degradation. The impact on liver function after short-term exposure to ethylene glycol appears to be quite minor.

The results from chronic-duration animal studies show that there are no adverse hepatic effects in rats fed a diet delivering 2,500 mg/kg/day of propylene glycol for 2 years (Gaunt et al. 1972). Based on these findings, it can be assumed that chronic oral exposures to moderately high levels of propylene glycol will not have adverse hepatic effects in humans. It is not clear if hepatotoxicity would result after an acute exposure to a high level of propylene glycol. Since levels of propylene glycol in the vicinity of a hazardous waste site would probably be low, it is unlikely that propylene glycol would induce adverse hepatic effects would occur in people living in the area.

Renal Effects. Adverse renal effects after ethylene glycol ingestion in humans can be observed during the third stage of ethylene glycol toxicity 24-72 hours after acute exposure. The hallmark of renal toxicity is the presence of birefringent calcium oxalate monohydrate crystals deposited in renal tubules and their presence in urine after ingestion of relatively high amounts of ethylene.glycol (Anonymous 1987; Blakeley et al. 1993; Chung and Tuso 1989; Factor and Lava 1987; Godolphin et al. 1980; Heckerling 1987; Parry and Wallach 1974; Rothman et al. 1986; Siew et al. 1975a; Underwood and Bennett 1973). In addition to birefringent oxalate crystals in the tubular lumens, other signs of nephrotoxicity can include focal tubular cell degeneration, atrophy, and tubular interstitial inflammation (Factor and Lava 1987). In a case study of a 3%year-old female who consumed 240 mL

of antifreeze (3,454 mg ethylene glycol/kg/day), crystalluria was not present upon hospital admission (about 12 hours after ingestion). Within 5 hours, excretion of calcium oxalate dihydrate crystals was evident, although monohydrate crystals became the primary form in the urine thereafter (2-3 hours) (Jacobsen et al. 1988). The presence of ethylene glycol metabolites-oxalic and glycolic acids-also contributes to nephrotoxicity. In the course of ethylene glycol intoxication, serum creatinine (Factor and Lava 1987; Spillane et al. 1991) and serum blood urea nitrogen (BUN) (Chung and Tuso 1989; Factor and Lava 1987) levels may be increased. If untreated, the degree of renal damage caused by high doses of ethylene glycol progresses and leads to hematmia (Anonymous 1987; Rothman et al. 1986; Underwood and Bennett 1973), proteinuria (Rothman et al. 1986), decreased renal function, oliguria, anuria (Mallya et al. 1986; Parry and Wallach 1974; Spillane et al. 1991; Woolf et al. 1992; Zeiss et al. 1989), and ultimately renal failure (Chung and Tuso 1989; Gordon and Hunter 1982; Jacobson et al. 1984; Mallya et al. 1986). These changes in the kidney are linked to acute tubular necrosis (Factor and Lava 1987), but normal or near normal renal function can return with adequate supportive therapy (Parry and Wallach 1974). In the majority of cases, the most effective therapy consists of hemodialysis and administration of ethanol as a substrate competitor of ethylene glycol for oxidative enzymes, leading to a decrease in the formation of toxic metabolites. Successful treatment of ethylene glycol poisoning has also been accomplished using 4-methyl pyrazole as a competitive substrate (Baud et al. 1987, 1988).

Rats receiving 1,400 mg/kg/day ethylene glycol in the drinking water for 3-29 days exhibited renal tubular oxalate deposits and/or crystalluria (Ebisuno et al. 1987; Khan et al. 1993), whereas in another study, enlarged kidneys were observed in Porton rats after 21 days of treatment with 999-1,110 mg/kg ethylene glycol in the drinking water (Rofe et al. 1986). No histopathological changes were observed in kidneys of mice after oral exposure to 1,000 mg/kg of ethylene glycol for up to 14 days (Hong et al. 1988). Neither was there any effect in male mice after 17 days oral treatment with 2,500 mg/kg/day (Harris et al. 1992). Renal damage leading to oliguria and renal failure occurred in dogs (Beckett and Shields 1971; Grauer et al. 1987) and cats (Penumarthy and Oehme 1975) after a single oral exposure to 4,880 or 10,743 mg/kg (dogs) and 4,440 mg/kg of ethylene glycol (cats). Dogs receiving a single dose of 10,600 mg/kg ethylene glycol as antifreeze or as reagent grade ethylene glycol in feed exhibited polyuria and azotemia, and renal failure (Dial et al. 1994). In dogs given a dose of 1,000-l ,360 mg/kg/day, there were no increases in serum BUN or creatinine, suggesting normal renal function (Hewlett et al. 1989). In monkeys receiving ethylene glycol in drinking water

(0.25-10% for 6-13 days), 5 of 7 animals given doses greater than 1,388 mg/kg/day had calcium oxalate crystals and evidence of necrosis in the kidney (Roberts and Siebold 1969).

Pregnant mice exposed orally to 1,500 mg/kg/day ethylene glycol during gestation exhibited no renal effects (Tyl 1989); rats exposed to 2,500 mg/kg/day during gestation exhibited increased relative kidney weight but no adverse histopathological changes (Neeper-Bradley 1990). Timed-mated rats were dosed by gavage on Gd 6-20 with 0, 250, 1,250, or 2,250 mg/kg/day ethylene glycol (NTP 1988). Treatment-related renal pathology was evident in the mid- and high-dose dams. In contrast, New Zealand White rabbits given 2,000 mg/kg/day ethylene glycol by gavage during gestation exhibited characteristic renal toxicity including oxalate crystals, epithelial and tubular necrosis, and degeneration of the cortical tubules (Tyl et al. 1993). Fischer 344 rats receiving up to 2,500 mg/kg/day ethylene glycol in the feed for 13 weeks exhibited oxalate nephrosis and renal failure at doses of 1,250 mg/kg/day and above (Melnick 1984). Mice treated under the same regimen exhibited mild nephrosis at 3,250 mg/kg/day, and regenerative hyperplasia of the tubular epithelium (Melnick 1984). After a l-year exposure, male Fischer 344 rats, exhibited oxalate nephrosis and nephritis at 1,000 mg/kg/day in the feed (DePass et al. 1986a; Woodside 1982); male mice and rats exhibited the same effects after exposure to 3,315 mg/kg/day ethylene glycol in the feed for 2 years (NTP 1992). These findings indicate that there may be dose-response differences in the renal effects of ethylene glycol exposure. The results also show that the relationship between oxalate crystals in the kidney and nephrotoxicity is not causal, although the formation of oxalate crystals greatly contributes to renal toxicity. It seems reasonable to conclude from these studies that acute human exposure to relatively high doses of ethylene glycol leads to renal toxicity, but that chronic exposure to the low levels typically found in the vicinity of hazardous waste sites poses little risk of renal toxicity.

No adverse renal effects were observed in cats fed a diet delivering a dose of 1,600 mg/kg/day of propylene glycol for 5 weeks (Christopher et al. 1989a). In the same study, however, cats exposed to 8,000 mg/kg/day of propylene glycol for 3 weeks developed polyuria, considered a less serious adverse effect. In another study, an equal number (5-6) of cats of both sexes w.ere fed 1,600 mg/kg/day propylene glycol for 5 weeks or a high dose diet containing 8,000 mg/kg/day for 22 days (Christopher et al. 1990b). Cats fed the low dose had no adverse clinical signs. Cats fed the high dose had moderate polyuria and polydipsia. Chronic exposure of both rats and dogs to 2,500 and 5,000 mg/kg/day, respectively, for 2 years, had no nephrotoxic effects in either species (Gaunt et al. 1972; Weil et al. 1971). These results indicate that exposure to low levels of propylene glycol that

may be present at hazardous waste sites are not likely to cause adverse renal effects in the human population living in the vicinity.

Endocrine Effects. CD-l mice fed up to 1,000 mg/kg/day ethylene glycol for 24 months showed no abnormal histopathology of the endocrine organs (DePass et al. 1986a).

Fischer 344 rats exhibited adrenocortical hemorrhage after a single oral dose of 23,500 mg/kg propylene glycol (Clark et al. 1979). However, no adverse effects on endocrine organs were noted in rats exposed to 2,500 mg/kg/day ethylene glycol for 2 years (Gaunt et al. 1972).

Dermal Effects. CD-l mice fed up to 1,000 mg/kg/day ethylene glycol for 24 months showed no abnormal dermal effects (DePass et al. 1986a).

Body Weight Effects. Pregnant CD rats and CD-l mice showed a decrease in body weight after oral exposure to doses 11,250 or 1,500 mg/kg/day on Gd 6-15 (Marr et al. 1992; Neeper-Bradley 1990; Price et al. 1985). Timed-mated rats were dosed by gavage on Gd 6-20 with 0, 250, 1,250, or 2,250 mg/kg/day ethylene glycol (NTP 1988). The high dose caused a significant decrease in dam weight on Gd 20 which was secondary to increased in utero death and which was not evident after delivery of the litter. However, in other studies, pregnant CD-l mice and New Zealand White rabbits showed no changes in body weight after oral exposure to 1,500 or 2,000 mg/kg/day ethylene glycol, respectively, on Gd 6-15 or 6-19 (Tyl 1989). There was no effect in male mice after 17 days oral treatment with 2,500 mg/kg/day (Harris et al. 1992). Male Fischer 344 rats showed a 10% decrease in body weight gain after exposure to 1,250 mg/kg/day ethylene glycol in the feed for 13 weeks (Melnick 1984), whereas male mice showed similar effects after exposure to 1,625 mg/kg/day via the diet (NTP 1992). In a 3-generation reproductive study, Fischer 344 rats showed no adverse effects on body weight after exposure to 1,000 mg/kg/day ethylene glycol in the feed (DePass et al. 1986b). After 1 year of exposure to 1,000 mg/kg/day ethylene glycol in the feed, male rats exhibited decreased body weight, but female rats did not (DePass et al. 1986a; Woodside 1982). CD-l micedid not exhibit any significant change in body weight after 24 months exposure to 1,000 mg/kg/day ethylene glycol in the feed (DePass et al. 1986a).

Rats given 2,942 mg/kg propylene glycol by gavage for 10 days exhibited a 41% reduction in body weight, whereas exposure for 20-30 days caused an increase body weight (Morshed et al. 1991a).

Dogs exposed to 5,000 mg/kg/day oral propylene glycol for 2 years showed no adverse effect on body weight (Weil et al. 1971).

Metabolic Effects. One of the major adverse effects following acute oral exposure of humans to ethylene glycol involves metabolic changes. These changes occur as early as 12 hours after ethylene glycol exposure. Ethylene glycol intoxication at doses of 1,628 mg/kg/day is accompanied by metabolic acidosis which is manifested by decreased pH and bicarbonate content of serum and other bodily fluids caused by accumulation of excess glycolic acid (Anonymous 1987; Berger and Ayzar 1981; Blakeley et al. 1993; Cheng et al. 1987; Chung and Tuso 1989; Gordon and Hunter 1982; Heckerling 1987; Jacobsen et al. 1988; Parry and Wallach 1974; Siew et al. 1975a, Spillane et al. 1991; Woolf et al. 1992; Zeiss et al. 1989). There is an inverse relationship between the decreasing plasma pH and increasing plasma glycolic acid concentrations (Clay and Murphy 1977). The normal level of bicarbonate of 24 mmovL can be depleted in cases of severe ethylene glycol intoxication to reach concentrations as low as 2 mmol/L (Jacobsen et al. 1984). This decrease in base concentration indicates that a similar quantity of acid has to be present to achieve such a depletion. Glycolic acid is the only acidic metabolite present in such quantities. Humans highly intoxicated with ethylene glycol had glycolate concentrations from 17 to 29 mm01 and <l mmo1 of glyoxalate and oxalate (Jacobsen et al. 1984). Similar observations were made in animals. Metabolic acidosis due to glycolate accumulation was observed after acute oral exposure of dogs to 1,000-1,360 mg/kg of ethylene glycol (Hewlett et al. 1989), and of rats to 1,000 mg/kg (Marshall 1982). These results indicate that glycolic acid is the major toxic metabolite causing metabolic acidosis, and that its high serum levels are likely responsible for systemic toxicity observed after ethylene glycol exposure.

Other characteristic metabolic effects of ethylene glycol poisoning are increased serum anion gap, increased osmolal gap, and hypocalcemia. Serum anion gap is calculated from concentrations of sodium, chloride, and bicarbonate and is elevated after ethylene glycol ingestion (Chung and Tuso 1989; Factor and Lava 1987; Heckerling 1987; Spillane et al. 1991; Zeiss et al. 1989). The increase in the anion gap correlates with the elevation in plasma glycolate levels (Jacobsen et al. 1984). Osmolal gap represents the difference between the measured and calculated osmolalities and is also elevated during ethylene glycol intoxication. The amount of ethylene glycol causing these effects ranged from 1,628 to 12,840 mg/kg/day (Chung and Tuso 1989; Heckerling 1987; Spillane et al. 1991). The normal value for osmolal gap in humans is less than 10 (Fligner et al. 1985). Hypocalcemia occurs when oxalate chelates with calcium ions forming insoluble calcium oxalate monohydrate crystals. This

affects the overall ion concentration and can lead to an imbalance of divalent ion concentrations (Zeiss et al. 1989). Dogs receiving a single dose of 10,600 mg/kg ethylene glycol as antifreeze or as reagent grade ethylene glycol in feed exhibited metabolic acidosis and hyperosmolality (Dial et al. 1994).

High levels of propylene glycol in the plasma can lead to an increase in the osmolal gap. Propylene glycol is oxidatively converted to lactic and pyruvic acids which, if present in sufficient amounts, contribute to a metabolic acidosis. However, acidosis from propylene glycol is not as severe as that due to ethylene glycol. In a case of acute propylene glycol poisoning (the amount ingested not specified), the patient developed metabolic acidosis (pH of 7.29) with an osmolal gap of 51 mmol/kg (reference concentration is <l0 mmol/kg) (Lolin et al. 1988). There is a possibility that this patient also ingested a large amount of ethanol since the serum ethanol level was 90 mg/dL. The level of propylene glycol was 400 mg/dL in the serum and 10 mg/dL in urine.

Rats given oral doses of propylene glycol up to 5,885 mg/kg showed an increase of blood lactate of 2.7 mmol/L, which was prevented by inhibition of propylene glycol metabolism (Morshed et al. 1989). Rabbits given an oral dose of 2,942 mg/kg showed a similar increase in blood lactate of 2.6 mmol/L (Morshed et al. 1991b). In neither study was there a decrease in blood pH, probably because lactic acidosis in clinical situations occurs only when lactate levels rise more than 5 mmol/L (Morshed et al. 1989). An equal number (5-6) of cats of both sexes were fed a diet containing 12% propylene glycol (low dose, 1,600 mg/kg/day) for 5 weeks, a dose equivalent to that found in commercial soft-moist cat foods, or a high-dose diet containing 41% propylene glycol (8,000 mg/kg/day) for 22 days (Christopher et al. 1990b). Pre-dosing observations were made such that each group of cats served as its own control. In the low dose cats, anion gap increased from 15.5 Meq/liter during the control period to 22.2 Meq/liter on day 24 of exposure. Total CO_2, decreased at the end of the dosing period. Plasma D-lactate increased 24-fold during the dosing period and was significantly correlated with anion gap. L-lactate decreased significantly but in a less dramatic fashion to 31% of control values. Serum sodium increased slightly with dosing, but there were no other notable changes in serum chemistry. In high-dose cats, plasma D-lactate increased rapidly (44-fold) during dosing.

Other Systemic Effects. In a single mating reproductive trial, female CD-l mice were orally exposed to 250-2,500 mg/kg/day ethylene glycol for 20 consecutive days (Harris et al. 1992). The female mice showed no treatment-related clinical signs.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located specifically regarding immunological effects in humans or animals after oral exposure to ethylene glycol. Conflicting data were found regarding white blood cell counts, which were normal (Underwood and Bennett 1973) or elevated (Spillane et al. 1991) in two cases of oral ethylene glycol intoxication in humans.

Similar observations were made in mice after acute oral exposure to ethylene glycol at 1,000 mg/kg (Hong et al. 1988). An increased neutrophil count was present in male but not female Fischer 344 rats orally exposed to 1,000 mg/kg/day ethylene glycol in the feed for 12 months (DePass et al. 1986a; Woodside 1982). In the same study, increased neutrophil count was not seen in female Fischer 344 rats orally exposed to 1,000 mg/kg/day of ethylene glycol for 2 years, or in male rats exposed to 200 mg/kg/day ethylene glycol for 2 years (DePass et al. 1986a; Woodside 1982). No effect on neutrophil count was observed in CD-l mice exposed to 1,000 mgkglday ethylene glycol in the feed for 12 months (DePass et al. 1986a). Currently, there is no evidence that acute oral exposure to high concentrations of ethylene glycol adversely affects immunological functions. Intermediate oral exposure to low concentrations of ethylene glycol that may be present in the vicinity of hazardous waste sites is not likely to produce adverse immunological effects in populations residing in the area.

No studies were located regarding immunological and lymphoreticular effects in humans after oral exposure to propylene glycol.

Cats fed 1.2 mg propylene glycol per gram of feed for 14 days showed increased haptoglobin concentration (Weiss et al. 1992). Dogs fed 5,000 mgkg/day propylene glycol for 2 years showed no adverse immunological effects (Weil et al. 1971).

The highest NOAEL values and all reliable LOAEL values for immunological and lymphoreticular effects in rats after intermediate-duration oral exposure to ethylene glycol are reported inTable 2-3 and plotted in Figure 2-3. The highest NOAEL value and the LOAEL value for immunological and lymphoreticular effects in dogs and cats for each duration category for propylene glycol after oral exposure are reported in Table 2-4 and plotted in Figure 2-4.

2.2.2.4 Neurological Effects

Adverse neurological reactions are among the first symptoms to appear in humans after ethylene glycol ingestion. These early neurotoxic effects are also the only symptoms attributed directly to ethylene glycol. Together with metabolic changes, they occur during the period of 30 minutes to 12 hours after exposure and are considered to be part of the first stage in ethylene glycol intoxication (Robinson and McCoy 1989; Vale 1979). In cases of acute intoxication, in which a large amount of ethylene glycol is ingested over a very short time period, there is a progression of neurological manifestations which, if not treated, may lead to convulsions and coma (Zeiss et al. 1989). Ataxia, slurred speech, and somnolence are common during the initial phase of ethylene glycol intoxication (Anonymous 1987; Parry and Wallach 1974; Zeiss et al. 1989), as are irritation, restlessness, and disorientation (Cheng et al. 1987; Factor and Lava 1987; Gordon and Hunter 1982; Rothman et al. 1986; Woolf et al. 1992). In a fatal case of ethylene glycol poisoning, a 22-year-old man was admitted to the hospital in a state of stupor 6 hours after ingesting 4,071 mg/kg of ethylene glycol. He vomited several times prior to admission, lost consciousness, and became comatose (Siew et al. 1975a).

Crystalline deposits of calcium oxalate in the walls of small blood vessels in the brain were found at autopsy in a man who died after acute ethylene glycol poisoning (Zeiss et al. 1989). Similar effects were observed in rats fed 2,500 mg/kg/day ethylene glycol for 13 weeks (Melnick 1984). Other neurological symptoms commonly encountered in cases of acute oral human exposure to ethylene glycol are semiconsciousness (Underwood and Bennett 1973) and unresponsiveness (Blakeley et al. 1993; Chung and Tuso 1989; Heckerling 1987; Spillane et al. 1991). More recently, several case reports described neurological symptoms associated with adverse effects of ethylene glycol on cranial nerves. These neurotoxic manifestations appear much later and according to some investigators constitute a fourth, late cerebral phase in ethylene glycol intoxication (Chung and Tuso 1989). Facial paralysis and bilateral optic nerve dysfunction were noted in a patient 13 days after ethylene glycol ingestion (Factor and Lava 1987). Delay in treatment may have contributed to the development of these symptoms; the patient was not treated until 3 days after ingesting ethylene glycol;.Severe cranial nerve dysfunction including nerves VII, IX, and X was noted in a man 5 days after he ingested 12,840 mg/kg of ethylene glycol (Spillane et al. 1991). In another case of ethylene glycol poisoning, bilateral facial paralysis and peripheral neurosensory hearing loss were observed in a patient 18 days after ingestion of 2,714 mg/kg of ethylene glycol; this effect was only partially reversible (Mallya et al. 1986).

Female Fischer 344 rats exhibited ataxia and coma prior to death after receiving 4,000 mg/kg ethylene glycol orally (Clark et al. 1979). Ethylene glycol neurotoxicity was also observed in cats given 4,440 mg/kg by gavage (Penumarthy and Oehme 1975). Neurological symptoms included abnormal gait, loss of reflexes, central nervous system depression (symptoms not specified), and convulsions. Similar signs of neurotoxicity were found in dogs after oral exposure to 4,880-10,743 mg/kg ethylene glycol (Beckett and Shields 1971; Dial et al 1994; Grauer et al. 1987). Calcium oxalate deposits were found in the brain blood vessels of rats after 13 weeks exposure to ethylene glycol in the feed (Melnick 1984).

Adverse neurological reactions were observed in patients who tested positive in a propylene glycol patch test after an acute oral challenge with 2-15 mL of propylene glycol (Hannuksela and Forstrom 1978). Although the observed neurotoxicity is attributed to propylene glycol, the study reports that this response was seen in allergic individuals. In a case of acute propylene glycol poisoning, neurotoxic symptoms included stupor and repetitive convulsions (Lolin et al. 1988). The study does not specify the amount of propylene glycol that caused neurotoxicity. Various degrees of propylene glycol neurotoxicity were also observed in a group of 16 outpatients of a neurology clinic after acute oral exposure to 887 mg/kg 3 times per day for at least 3 days, using a formulation containing phenytoin and ethanol (Yu et al. 1985). Very severe mental symptoms (not specified) were observed in one patient who had the highest overall propylene glycol plasma concentration, although patients with lower plasma propylene glycol levels showed similar neurotoxicity. The estimated half-life of propylene glycol is 3.8 hours. This means that there is a measurable accumulation of propylene glycol if it is ingested in the course of a multiple-dosing regimen (Yu et al. 1985). The limitation of the study is that it does not specify if the observed propylene glycol effects may have been associated with the neurological problems already present in those patients or with concomitant ingestion of ethanol.

In a study of oral LD_{50} values using propylene glycol, lethargy and coma were observed prior to death in rats (Clark et al. 1979). An equal number (5-6) of cats of both sexes were fed a diet containing 12% propylene glycol (low dose, 1,600 mg/kg/day) for 5 weeks, a dose equivalent to that found in commercial soft-moist cat foods, or a high dose diet containing 41% propylene glycol (8,000 mg/kg/day) for 22 days (Christopher et al. 1990b). Pre-dosing observations were made such that each group of cats served as its own control. Animals were observed for signs of toxicity. Cats receiving the low dose showed no clinical signs of toxicity. Cats receiving the high dose developed decreased activity, mental depression [author's words], and slight to moderate ataxia. These cats had

high levels (44-fold higher than control) of D-lactate, thought to contribute to central nervous system toxicity. On the basis of this information, adverse neurological reactions due to exposure to low levels of propylene glycol possibly present at hazardous waste sites are very unlikely.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category for ethylene glycol after oral exposure are reported in Table 2-3, and plotted in Figure 2-3. The LOAEL value for neurological effects in rats for acute-duration category oral exposure propylene glycol is reported in Table 2-4 and plotted in Figure 2-4.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to ethylene glycol.

Results from an oral study done in mice are inconclusive. Histopathology done on testes from mice treated with 200, 400, and 1,000 mg/kg of ethylene glycol revealed marked loss of spermatogenic epithelium in a portion of the seminiferous tubules (Hong et al. 1988). The study does not indicate if one or all three doses of ethylene glycol induced this adverse effect. This effect was restricted to spermatogenic cells and did not involve Sertoli or interstitial cells. However, mice receiving 4,000 mg/kg/day ethylene glycol orally for 5 weeks did not show any pathological changes in the testis (Nagano et al. 1984). In a single mating reproductive trial, female CD-l mice were orally exposed to 250-2,500 mg/kg/day ethylene glycol for 20 consecutive days (Harris et al. 1992). On the eighth day of exposure, the females were cohabited with males that had been treated for 17 days. Females exposed to 2,500 mg/kg/day ethylene glycol had few live fetuses, more dead implants, and more litters totally resorbed. Male mice showed no treatment-related effects on the reproductive system (Harris et al. 1992). In a continuous breeding study done in CD-l mice (Lamb et al. 1985), intermediate exposure to 1% ethylene glycol in drinking water slightly decreased the fertility of the exposed parental and F_1 generations.

Dietary exposure of pregnant Fischer 344 rats to ethylene glycol (40-1,000 mg/kg/day) did not affect total implantation, or litter size (Maronpot et al. 1983). Price et al. (1985) treated rats and mice orally with doses of 1,250-5,000 mg/kg/day and 750-3,000 mg/kg/day, respectively, of ethylene glycol.

Increased postimplantation loss was observed in rats at 5,000 mg/kg/day, and in mice at 750 mg/kg/day (Price et al. 1985).

Oral administration of 50-1,500 mg/kg/day ethylene glycol to pregnant CD-l mice on Gd 6-15 had no effect on postimplantation viability (Tyl 1989). Pregnant mice given 11,090 mg/kg/day ethylene glycol on Gd 7-14 and allowed to deliver their litters exhibited a decrease in the number of viable litters, live pups per litter, and pup survival to post-parturition day (ppd) 2.5 (Schuler et al. 1984). Oral administration of 150-2,500 mg/kg/day ethylene glycol to pregnant Sprague-Dawley rats on Gd 6-15 caused no adverse effect on postimplantation viability (Neeper-Bradley 1990). However, in another study, timed-mated rats were dosed by gavage on Gd 6-20 with 0, 250, 1,250, or 2,250 mg/kg/day ethylene glycol (NTP 1988). Litters (38-49 per group) were fostered to untreated dams on ppd 1 and evaluated for growth, viability, developmental landmarks, locomotor activity, and learning. Live litter size and postnatal viability through ppd 4 were decreased at 2,250 mg/kg/day. Tyl et al. (1993) administered 100-2,000 mg/kg/day ethylene glycol by gavage to pregnant New Zealand White rabbits on Gd 6-19, and detected no effect on implant viability.

Fischer 344 rats were fed 40, 200, or 1,000 mg/kg/day ethylene glycol via the feed for 3 generations (DePass et al. 1986b). No changes in reproductive indices, including fertility, prenatal survival, litter size, and postnatal survival were found as a result of treatment. In an accompanying 2-year study, reproductive organs of Fischer 344 rats and CD-l mice fed up to 1,000 mg/kg/day via the feed showed no abnormal histopathology (DePass et al. 1986a; Woodside 1982).

No studies were located regarding reproductive effects in humans after oral exposure to propylene glycol.

Pregnant female Swiss mice were given 10,000 mg/kg/day propylene glycol by mouth on Gd 8-12 (Kavlock et al. 1987). There was no effect of treatment on their ability to produce live pups, or on the survival of those pups. The effects of propylene glycol on reproduction of Swiss (CD-l) mice were tested in a protocol which permitted continuous breeding during a specified interval (NTP 1985). Propylene glycol in drinking water at doses of 0, 1.0, 2.5, and 5.0% yielded mean exposures of 0, 1,819, 4,796, and 10,118 mg/kg/day, based on water consumption. Animals were treated during a l-week pre-cohabitation period and a 14-week monogamous cohabitation ‘period. Any offspring produced during the cohabitation period were examined, sexed, weighed, and killed to allow

continuous mating of the parental generation. At the end of the cohabitation period, males and females were separated, and the females were allowed to deliver and raise the last litter to weaning. Propylene glycol had no adverse effects on any measure of reproduction, including number of litters, litter size, pup weight, or sex ratio. There was no effect on the reproductive capacity of offspring from the high dose group.

The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category for ethylene glycol after oral exposure are reported in Table 2-3 and plotted in Figure 2-3. The highest NOAEL values for reproductive effects in each species and duration category for propylene glycol after oral exposure are reported in Tables 2-4 and plotted in Figure 2-4.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to ethylene glycol.

Dietary exposure of pregnant Fischer 344 rats to ethylene glycol (40-1,000 mg/kg/day) did not affect total implantation, fetal length, fetal weight, or litter size (Maronpot et al. 1983). Vertebral malformations and rib alterations were present in both treated and control animals, but ethylene glycol did not increase the incidence of these malformations. However, there were statistically significant increases in the incidences of poorly ossified and nonossified vertebral centers in fetuses of dams receiving 1,000 mg/kg/day of ethylene glycol; the authors did not consider these to be major malformations. These findings, plus a number of external malformations, were seen. in Sprague-Dawley-derived rats and Swiss CD-l mice (Price et al. 1985) treated orally with doses of 1,250-5,000 mg/kg/day and 750-3,000 mg/kg/day, respectively, of ethylene glycol. The percentage of malformed live fetuses per litter and/or the percentage of litters with malformed fetuses were significantly elevated in all groups treated with ethylene glycol (Price et al. 1985). Reduced fetal body weight was observed at 2,500 mg/kg/day in rats, whereas reduced litter size was observed at 5,000 mg/kg/day (Price et al. 1985).

Oral administration of 50-1,500 mg/kg/day ethylene glycol to pregnant CD-l mice on Gd 6-15 caused an increase in total malformations at 500 mg/kg/day, although the increase could not be associated with individual external, visceral, or skeletal malformations (Tyl 1989). Pregnant mice given

11,090 mg/kg/day ethylene glycol on Gd 7-14 and allowed to deliver their litters exhibited a decrease in the number of viable litters, live pups per litter, pup survival, pup body weight, and body weight gain to post-parturition day (ppd) 2.5 (Schuler et al. 1984). Livebom pups of pregnant CD-l mice that were orally treated with 250-2500 mg/kg/day ethylene glycol on Gd 8-14 exhibited decreased body weight at 2,500 mg/kg/day on ppd 1 and 4 (Harris et al. 1992). Ethylene glycol at 2,500 mg/kg/day administered to pregnant Sprague-Dawley rats on Gd 6-15 caused an increase in the incidence of skeletal malformations and delayed ossification, and a decrease in fetal body weight (Marr et al. 1992). Oral administration of 150-2,500 mg/kg/day ethylene glycol to pregnant Sprague-Dawley rats on Gd 6-15 showed an increase in the incidence of individual skeletal malformations, including missing ribs and missing thoracic arches at 1,000 mg/kg/day (Neeper-Bradley 1990). Timed-mated rats were dosed by gavage on Gd 6-20 with 0, 250, 1,250, or 2,250 mg/kg/day ethylene glycol (NTP 1988). Litters (38-49/group) were fostered to untreated dams on ppd 1 and evaluated for growth, viability, developmental landmarks, locomotor activity, and learning. Decreased pup weight was observed at the high dose. Live litter size, pup weight, and postnatal viability through ppd 4 were decreased at 2,250 mg/kg/day. A significant increase in axial skeletal malformations was seen in pups from the 2,250 mg/kg/day. No adverse effects were noted in wire grasp, preweaning exploratory behavior, or visual discrimination tasks. Tyl et al. (1993) administered 100-2,000 mgAsg/day ethylene glycol by gavage to pregnant New Zealand White rabbits on Gd 6-19, and detected no effect on developmental parameters.

No studies were located regarding developmental effects in humans after oral exposure to propylene glycol.

Pregnant female Swiss mice were given 10,000 mg/kg/day propylene glycol by mouth on Gd 8-12 (Kavlock et al. 1987). There was no effect of treatment on their ability to produce live pups, or on the survival of those pups. The effects of propylene glycol on reproduction of Swiss (CD-l) mice were tested in a protocol which permitted continuous breeding during a specified interval (NTP 1985). Propylene glycol in drinking water at doses of 0, 1.0, 2.5, and 5.0% yielded mean exposures of 0, 1,819, 4,796, and 10,118 mg/kg/day, based on water consumption. Animals were treated during a l-week pre-cohabitation period and a 14-week monogamous cohabitation period. Any offspring produced during the cohabitation period were examined, sexed, weighed, and killed to allow continuous mating of the -parental generation. At the end of the cohabitation period, males and females were separated, and the females were allowed to deliver and raise the last litter to weaning.

Propylene glycol had no adverse effects on any measure of reproduction, including number of litters, litter size, pup weight, or sex ratio. There was no effect on the reproductive capacity of offspring from the high dose group.

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category for ethylene glycol after oral exposure are reported in Table 2-3 and plotted in Figure 2-3. The highest NOAEL values for developmental effects in each species and duration category for propylene glycol after oral exposure are reported in Table 2-4 and Figure 2-4.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to ethylene glycol. In Fischer 344 rats that received oral doses of 40, 200, and 1,000 mg/kg/day for 3 generations, there were no dominant lethal mutations (DePass et al, 1986b).

No studies were located regarding genotoxic effects in humans or animals after oral exposure to propylene glycol.

Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer effects in humans after oral exposure to ethylene glycol.

A 2-year oral exposure study in mice and rats (40, 200, and 1,000 mg/kg/day of ethylene glycol) produced no evidence of an oncogenic effect (DePass et al. 1984, 1986a; Woodside 1982). Furthermore, a recent 2-year. dietary study in mice indicated a lack of carcinogenic effects (NTP 1992).

Because of information available, it is reasonable to conclude that oral exposures to ethylene glycol incurred from waste site sources pose negligible risks of cancer.

No studies were located regarding cancer effects in humans after oral exposure to propylene glycol.

In a dietary study of chronic oral exposure of rats to 2,500 mg/kg/day, there were no treatment-related increases in neoplasms (Gaunt et al. 1972). Based on this information, its long history of use in consumer products, and structural activity considerations, it is extremely unlikely that exposure to levels of propylene glycol near hazardous waste sites would influence the incidence of cancer in the population living in the vicinity.

2.2.3 Dermal Exposure

Dermal exposure, through activities such as changing antifreeze, is the most likely route of exposure to ethylene glycol, but dermal exposure is not likely to lead to toxic effects.

Dermal exposure to propylene glycol most likely occurs through contact with cosmetics or drugs.

2.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to ethylene glycol or propylene glycol. Therefore, no LOAELs for death following dermal exposure could be established. Based on the absence of data in the literature, it is unlikely that sufficient amounts of ethylene glycol or propylene glycol would be present or inhaled near hazardous waste sites to cause death among people living in the area.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, body weight, or metabolic effects in humans or respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal; endocrine, ocular, or metabolic effects in animals after dermal exposure to ethylene glycol.

No studies were located regarding gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, ocular, or body weight effects in humans, or respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, body weight, or metabolic effects in animals after dermal exposure to propylene glycol.

The highest NOAEL values for systemic effects in each species and duration category for ethylene glycol after dermal exposure are reported in Table 2-5. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category for propylene glycol after dermal exposure are reported in Table 2-6.

Respiratory Effects. Acute respiratory acidosis and cardiorespiratory arrest occurred in an 8-month-old infant with second- and third-degree burns after acute dermal treatment with silver sulfadiazine containing a high amount of propylene glycol. The dose of propylene glycol was 9,000 mg/kg/day (Fligner et al. 1985). Due to the high dose of propylene glycol, and the possible concomitant effects ,of both the bum injury and the sulfadiazine therapy, the actual source of the respiratory effect in this infant could not be determined, although propylene glycol can not be ruled out as the causative agent.

Cardiovascular Effects. Very limited and conflicting information is available for humans on cardiovascular effects after dermal exposure to propylene glycol. An &month-old infant suffered cardiorespiratory arrest after four dermal exposures to propylene glycol in a silver sulfadiazine medication (Fligner et al. 1985). Due to the high dose of propylene glycol, and the possible concomitant effects of both the bum injury and the sulfadiazine therapy, the actual source of the cardiorespiratory effect in this infant could not be determined, although propylene glycol can not be ruled out as the causative agent. Other studies of propylene glycol in humans did not evaluate cardiovascular effects.

It appears that acute exposure to very high levels of propylene glycol may cause adverse cardiovascular effects, but it is unlikely that such exposures could occur as a result of being in the vicinity of hazardous waste sites.

Hepatic Effects. Pregnant female mice exposed to 3,549 mg/kg/day ethylene glycol for 6 hours per day on Gd 6-15 by occluded dermal application showed no hepatic effects (Tyl 1988b).

Renal Effects. Pregnant female mice exposed to 3,549 mg/kg/day ethylene glycol for 6 hours per day on Gd 6-15 by occluded dermal application showed no renal effects (Tyl 1988b).

TABLE 2-5. Levels of Significant Exposure to Ethylene Glycol - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
ACUTE EXPOSURE						
Systemic						
Mouse (CD-1)	10 d Gd 6-15 6 hr/d	Hepatic	3549 mg/kg F			Tyl 1988b
		Renal	3549 mg/kg F			
		Dermal	3549 mg/kg F			
		Bd Wt	3549 F			
Rabbit (New Zealand)	once	Dermal	0.11 gm F			Clark et al. 1979
Reproductive						
Mouse (CD-1)	10 d Gd 6-15 6 hr/d		3549 mg/kg			Tyl 1988b
Developmental						
Mouse (CD-1)	10 d Gd 6-15 6 hr/d		3549 mg/kg			Tyl 1988b

Bd Wt = body weight; d = day(s); F = female; Gd = gestational day; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; NOAEL = no-observable-adverse-effect level

TABLE 2-6. Levels of Significant Exposure to Propylene Glycol - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference
ACUTE EXPOSURE						
Systemic						
Human	5 d 1x/d	Hemato	6100 mg/kg			Commens 1990
Human	70 hr >1x/d	Resp			9000 M mg/kg (acute respiratory acidosis)	Fligner et al. 1985
		Cardio			9000 M mg/kg (cardiorespiratory arrest)	
		Metab			9000 M mg/kg (increased osmolal gap)	
Human	20-24 h	Dermal		3.2% (irritation reaction)		Hannuksela et al. 1975
Human	48 hr once	Dermal		10 mg (50% solution, skin edema and erythema)		Kinnunen and Hannuksela 1989
Human	48 hr once	Dermal		0.2 mg (1% solution, erythema and edema)		Kinnunen and Hannuksela 1989
Human	7 d 2x/d	Dermal	104 M mg			Trancik and Maibach 1982
Human	once 48 hrs	Dermal		2.5% (erythema, induration, vesiculation)		Warshaw and Herrmann 1952
Human	48 hr once	Dermal	15 mg M	31 mg M (faint, patchy erythema with edema)		Willis et al. 1988
Human	48 hr once	Dermal		16 mg M ("basket weave" pattern to stratum corneum)		Willis et al. 1989

TABLE 2-6. Levels of Significant Exposure to Propylene Glycol - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
Rabbit (New Zealand)	once	Dermal	0.52 F gm			Clark et al. 1979
Rabbit (New Zealand)	once	Dermal	0.1 gm F			Clark et al. 1979
Immunological/Lymphoreticular						
Human	20-24 hr			3.2% (allergic reaction)		Hannuksela et al. 1975
Neurological						
Human	70 hr >1x/d				9000 M mg/kg (hypoxic encephalopathy)	Fligner et al. 1985
INTERMEDIATE EXPOSURE						
Systemic						
Human	21-22 d	Dermal		207 mg M (erythema)		Trancik and Maibach 1982

Cardio = cardiovascular; d = day(s); F = female; Hemato = hematological; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; M = male; Metab = metabolic; NOAEL = no-observable-adverse-effect level; Resp = respiratory; x = times

2. HEALTH EFFECTS

Dermal Effects. Skin irritation was minimal in New Zealand White rabbits 24-72 hours after application of 0.55 grams ethylene glycol to shaved skin (Clark et al. 1979). Pregnant female mice exposed to 3,549 mg/kg/day ethylene glycol for 6 hours per day on Gd 6-15 by occluded dermal application showed no dermal effects (Tyl 1988b).

Propylene glycol does not seem to have significant irritative properties. Skin testing of 42 healthy volunteers showed that 100% propylene glycol caused faint, patchy erythema with edema in 40% of the tested subjects (Willis et al. 1988). In another study, an acute dermal exposure of eczema patients to 0.2 and 22.8 mg/cm2 of propylene glycol caused skin edema and erythema in 3.8% of the 823 patients that were skin tested (Kinnunen and Hannuksela 1989). On the basis of-the findings from these studies, the authors concluded that propylene glycol has marginal irritant properties. However, some cases of sensitivity have been recorded in the literature. A 51-year-old woman developed a severe itchy erythematous vesicular dermatitis of the upper lip, nose and adjoining right cheek after applying a cream containing 10% propylene glycol (Corrazza et al. 1993). A patch test revealed a sensitivity to propylene glycol. In a test of 1,226 patients, applying 5% propylene glycol in Vaseline, or 10, 30, or 50% in water, caused approximately 208 patients to show some reaction (Aberer et al. 1993). Of these 208 patients, 195 exhibited some form of irritation, whereas only 13 exhibited an allergic reaction (Aberer et al. 1993). The mechanism of the reaction is not understood, but electron microscopy revealed that propylene glycol causes hydration of cornea1 cells producing a characteristic "basket weave" pattern in the stratum comeum (Willis et al. 1989). In order to determine if propylene glycol can also evoke a hypersensitivity reaction, a total of 15 patients who had positive skin reactions to propylene glycol were exposed to an acute oral propylene glycol challenge (Hannuksela and Forstrijm 1978). The hypersensitivity reaction that developed consisted of exanthem and cleared within 36-48 hours without any medications.

During 1951 and 1952, propylene glycol was applied in a covered patch test to the normal skin of 866 patients (Warshaw and Herrmann 1952). The test sites were examined 48 hours after application of the patches. Undiluted propylene glycol (Brand A, B, and C), and aqueous dilutions-of Brand A (2.5, 10, and 50%) were tested. Related compounds, including glycerine, and carbowax 1,500, were also tested. Propylene glycol was also applied directly to the skin of some individuals with a glass rod for 20 seconds. The application site was left uncovered. In many of the patients, the patch tests were repeated, but in different locations. When possible, the patients were re-tested after a period of several months. Several patients who reacted to propylene glycol were re-tested with exposure to propylene

glycol and dry heat; female patients who reacted to propylene glycol received lipsticks containing propylene glycol for trial use. Positive results were observed in 138 (15.7%) of the skin patch tests of propylene glycol. The reactions ranged from simple erythema to erythema with induration and vesiculation. No differences were noted in reactions to different brands of propylene glycol. Twenty-three persons with reactions to pure propylene glycol were tested with 50 and 10% dilutions. In general, the reaction to propylene glycol decreased with decreasing concentration. Only 5 of 23 showed any reaction to 10% propylene glycol, and only showed simple erythema. One of three persons tested with 2.5% propylene glycol had a positive reaction. Sixteen patients with positive reactions to the propylene glycol patch test were further patch-tested with glycerine and carbowax 1500, yielding 1 positive reaction to carbowax 1500, and a questionable positive reaction to glycerine. Sixteen patients with positive reactions to the patch test with propylene glycol were retested by simple application of propylene glycol. No positive reactions were observed. The incidence of positive reactions to propylene glycol appeared to fluctuate with the season, and was significantly higher during the cooler and less humid months (14-22% from October to June, 6% from July to September). In 23 of the positive reacting patients, the patch tests with propylene glycol were repeated after a period of 2-12 months. Seventeen of 23 patients showed a positive response, while the other 6 showed no response. Repeated testing with increased heat and moisture, reactivity tended to decrease. One of 15 female patients with a positive reaction to the propylene glycol patch test was also reactive to lipstick containing propylene glycol which was applied to the lips.

Propylene glycol was tested on the skin of 1,556 patients with eczema using a chamber on the back of the patients (Hannuksela et al. 1975). Undiluted propylene glycol was applied to the backs of the patients and left there for 20-24 hours. Readings of the exposure area were made 1, 2, and 4-5 days after application of the chemical. Reactions with redness, with or without infiltration peaking on the first day were considered irritant reactions. Reactions with infiltration with or without vesiculation extending to a considerably larger area than the test area, with the maximum occurring on the second day or later were considered' allergic. Forty-two positive reactors were subjected to patch tests with 3.2, 10, or 32% aqueous propylene glycol. Fifteen patients with allergic reactions to propylene glycol. applied undiluted propylene glycol to their armpits 3 times daily for 4 days. Of the patients tested with undiluted propylene glycol, 12.5% showed positive reactions. Of these, 70% were of primary irritation, and 30% were allergic in appearance. Seasonal variation was observed, with more cases observed in the winter. Forty-two cases of positive reactions to undiluted propylene glycol were retested with aqueous dilutions of the compound. Twelve of 42 showed a positive reaction to 10%,

and 9 of 42 had a reaction to 3.2%; 20 of 42 cases reacted to the 32% solution. Eleven of 15 patients who applied propylene glycol to their armpits had no reaction. The 4 reacting patients exhibited itching 4-10 hours and eczema within 24 hours. The symptoms reached their peak at 48 hours and disappeared after 3-5 days. Three of these patients used undiluted propylene glycol and one patient used 10% propylene glycol. In this latter patient, examination of the skin of a lo-hour-old reaction revealed no change in the epidermis, but perivascular infiltration in the dermis, indicative of an allergic reaction.

A 21-day cumulative irritation test was conducted using propylene glycol (Trancik and Maibach 1982). Ten Caucasian males with healthy skin received dermal applications of 207 mg propylene glycol (USP) on their backs in the same spot every day for 21 days. The application site was occluded with gauze and tape for 24 hours following application. Daily readings of test site were conducted at the time the patches were removed. Scoring ranged from no visible reaction to intense erythema with edema and vesicular erosion. In the 21-day cumulative irritation test, only one subject presented with a reaction, which was rated as equivocal irritation, on 20 of the test. All other subjects in the test had no reaction. Results of the 21-day cumulative irritation test indicates that propylene glycol is at least a minimal irritant.

There are few studies of dermal effects of propylene glycol in animals. New Zealand White rabbits exposed to 0.52 g of propylene glycol on skin showed little or no irritation after 72 hours (Clark et al. 1979).

These findings, plus a long history of safe use in medicine, indicate that prolonged dermal exposure to the low levels of propylene glycol present at hazardous waste sites is very unlikely to cause hypersensitivity or other skin reactions in the human population living in the vicinity.

Ocular Effects. Little or no eye irritation was noted after instillation of 0.11 g ethylene glycol in the eye of rabbits (Clark et al. 1979).

Body Weight Effects. Pregnant CD-l mice showed no changes in body weight after exposure to 3,549 mg/kg/day ethylene glycol for 6 hours per day on Gd 6-15 by occluded dermal application (Tyl 1988b).

Metabolic Effects. High levels of propylene glycol in the plasma can lead to an increase in the osmolal gap. Propylene glycol is oxidatively converted to lactic and pyruvic acids which, if present in sufficient amounts, contribute to a metabolic acidosis. However, acidosis from propylene glycol is not as severe as that due to ethylene glycol. Increased osmolal gap was found in two cases of acute dermal exposure to propylene glycol. An S-month-old infant with a severe bum was topically treated with 9,000 mg/kg/day of propylene glycol used as a vehicle for silver sulfadiazine (Fligner et al. 1985). The osmolal gap reached a maximum of 130 rnilliosmoles/kg 14 days after the treatment started, while serum propylene glycol level peaked at 1,059 mg/dL. Due to the high dose of propylene glycol, and the possible concomitant effects of both the bum injury and the sulfadiazine therapy, the actual source of the metabolic effect in this infant could not be determined, although propylene glycol can not be ruled out as the causative agent. The bum injury may have contributed to the increased absorption of propylene glycol and hence, the hyperosmolality. However, in another study of acute dermal propylene glycol exposure of 12 adults to 6,100 mg/kg/day for 5 days, propylene glycol had no effect on either serum osmolality or lactic acid levels (Commens 1990). Although the results of these studies are not conclusive, it seems that increased lactate levels leading to acidosis and increased osmolality may develop in humans in the event high levels of propylene glycol are absorbed into the blood stream.

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans or animals after dermal exposure to ethylene glycol.

No studies were located regarding immunological and lymphoreticular effects in animals after dermal exposure to propylene glycol.

Since propylene glycol is widely used as a vehicle for dermally applied medications, several studies investigated its potential as both an irritant and contact allergen. Skin testing of 42 healthy volunteers showed that 100% propylene glycol caused faint, patchy erythema with edema in 40% of the tested subjects (Willis et al. 1988). In another study, an acute dermal exposure of eczema patients to 0.2 and 22.8 mg/cm’ of propylene glycol caused skin edema and erythema in 3.8% of the 823 patients that were skin tested (Kinnunen and Hannuksela 1989). On the basis of the findings from these two studies, the authors concluded that propylene glycol has marginal irritant properties. However, some

cases of sensitivity have been recorded in the literature. A 51-year-old woman developed a severe itchy erythematous vesicular dermatitis of the upper lip, nose, and adjoining right cheek after applying a cream containing 10% propylene glycol (Corrazza et al. 1993). A patch test revealed a sensitivity to propylene glycol. In a test of 1,226 patients applying 5% propylene glycol in Vaseline, or 10, 30, or 50% in water resulted in approximately 208 patients showing some reaction (Aberer et al. 1993). Of these 208 patients, 195 exhibited some form of irritation, whereas only 13 exhibited an allergic reaction (Aberer et al. 1993). The mechanism of the reaction is not understood, but electron microscopy revealed that propylene glycol causes hydration of comeal cells producing a characteristic "basket weave" pattern in the stratum comeum (Willis et al. 1989): In order to determine if propylene glycol can also evoke a hypersensitivity reaction, a total of 15 patients who had positive skin reactions to propylene glycol were exposed to an acute oral propylene glycol challenge (Hannuksela and Forström 1978). The hypersensitivity reaction that developed consisted of exanthem and cleared within 36-48 hours without any medications. Propylene glycol was tested on the skin of 1,556 patients with eczema using a chamber on the back of the patients (Hannuksela et al. 1975). Undiluted propylene glycol was applied to the backs of the patients and left there for 20-24 hours. Readings of the exposure area were made 1, 2, and 4-5 days after application of the chemical. Reactions with redness, with or without infiltration peaking on the first day were considered irritant reactions. Reactions with infiltration with or without vesiculation extending to a considerably larger area than the test area, with the maximum occurring on the second day or later were considered allergic. Forty-two positive reactors were subjected to patch tests with 3.2, 10, or 32% aqueous propylene glycol. Fifteen patients with allergic reactions to propylene glycol applied undiluted propylene glycol to their armpits 3 times daily for 4 days. Of the patients tested with undiluted propylene glycol, 12.5% showed positive reactions. Of these, 70% were of primary irritation, and 30% were allergic in appearance. Seasonal variation was observed, with more cases observed in the winter. Forty-two cases of positive reactions to undiluted propylene glycol were retested with aqueous dilutions of the compound. Twelve of 42 cases showed a positive reaction to lo%, and 9 of 42 cases had a reaction to 3.2%; 20 of 42 cases reacted to the 32% solution. Eleven of 15 patients who applied propylene glycol to their armpits had no reaction. The 4 reacting patients exhibited itching 4-10 hours and eczema within 24 hours. The symptoms reached their peak at 48 hours and disappeared after 3-5 days. Three of these patients used undiluted propylene glycol and one patient used 10% propylene glycol. In this latter patient, examination of the skin of a lo-hour-old reaction revealed no change in the epidermis, but perivascular infiltration in the dermis, indicative of an allergic reaction.

A 22-day sensitization procedure was conducted using propylene glycol (Trancik and Maibach 1982). For the sensitization procedure, 203 Caucasian males with healthy skin received dermal doses of 207 mg propylene glycol on their backs on Mondays, Wednesdays, and Fridays for 22 days, resulting in a total of 10 doses. The application site was occluded for 48-72 hours (i.e., covered between doses). The test sites were read when the patches were changed. The application site was occluded with gauze and tape for 24 hours following application. Daily readings of test site were conducted at the time the patches were removed. Scoring ranged from no visible reactionto intense erythema with edema and vesicular erosion. In addition, minimal glazing of the skin (roughness) was added to the scoring list. Two weeks after the sensitization phase, a challenge dose was applied to previously untested skin and occluded for 48-72 hours. Rechallenge was performed at 2-week intervals. In the sensitization test, equivocal responses were noted, but no reaction more than equivocal was observed. At the challenge, 19 of 203 showed a positive response. Upon rechallenge, five exhibited an increase in response. The sensitization test indicates that propylene glycol might be a sensitizer.

These findings plus a long history of safe use in medicine indicate that prolonged dermal exposure to the low levels of propylene glycol present at hazardous waste sites is very unlikely to cause hypersensitivity reactions in the human population living in the vicinity.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals after dermal exposure to ethylene glycol.

No studies were located regarding neurological effects in animals after dermal exposure to propylene glycol.

Adverse neurological reactions were observed in patients who tested positive in a propylene glycol patch test after an acute oral challenge with 2-15 mL of propylene glycol (Hannuksela and Forstrom 1978). Although the observed neurotoxicity is attributed to propylene glycol, the study reports that this response was seen in allergic individuals. An 8-month-old infant with a severe bum was topically treated with 9,000 mg/kg/day of propylene glycol used as a vehicle for silver sulfadiazine (Fligner et al. 1985). After developing respiratory acidosis, the infant experienced cardiac arrest and was resuscitated. Subsequent neurological examination revealed hypoxic damage, which was evident by

persistent hypoxic encephalopathy. Due to the high dose of propylene glycol, and the possible concomitant effects of both the bum injury and the sulfadiazine therapy, the actual source of the respiratory effect and subsequent neurological damage in this infant could not be determined, although propylene glycol can not be ruled out as the causative agent.

The LOAEL value for neurological effects in humans for acute effects for propylene glycol after dermal exposure is reported in Table 2-6.

2.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after dermal exposure to ethylene glycol.

Pregnant CD-l mice exposed to ethylene glycol at doses up to 3,549 mg/kg on Gd 6-15 by occluded dermal application exhibited no adverse reproductive effects (Tyl 1988b).

No studies were located regarding reproductive effects in humans or animals after dermal exposure to propylene glycol.

The highest NOAEL value for reproductive effects in mice for the acute-duration category for ethylene glycol after dermal exposure are reported in Table 2-5

2.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans after dermal exposure to ethylene glycol.

Pregnant CD-l mice exposed to ethylene glycol at doses up to 3,549 mg/kg on Gd 6-15 .by occluded dermal application exhibited no adverse developmental effects, including fetal weight and morphological development (Tyl 1988b).

No studies were located regarding developmental effects in humans or animals after dermal exposure to propylene glycol.

The highest NOAEL value for developmental effects in mice for the acute-duration category for ethylene glycol after dermal exposure is reported in Table 2-5.

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after dermal exposure to ethylene glycol or propylene glycol.

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding cancer effects in humans or animals after dermal exposure to ethylene glycol.

No studies were located regarding cancer effects in humans after dermal exposure to propylene glycol.

No increase in tumors was observed after twice weekly applications of propylene glycol to the skin of Swiss mice for 120 weeks, at doses up to 2 mg (Stenback and Shubik 1974). Based on this information, its long history of use in consumer products, and stmctural activity considerations, it is extremely unlikely that exposure to levels of propylene glycol near hazardous waste sites would influence the incidence of cancer in the population living in the vicinity.

2.3 TOXICOKINETICS

The toxicokinetics of ethylene glycol is fairly well understood. Data from inhalation studies are relatively scarce; dermal studies are somewhat more numerous. Most of the kinetic data for ethylene glycol comes from oral exposures. Absorption, distribution, metabolism, and excretion have been monitored for ethylene glycol. Production of toxic metabolites is critical to the toxicity of ethylene glycol. These aspects are discussed below.

The toxicokinetics of propylene glycol is less well defined. Dermal data are most abundant for propylene glycol. Due to the relatively nontoxic nature of the compound, kinetic data are somewhat scarce. Available information is discussed below.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No kinetic data for absorption in humans or animals of ethylene glycol or propylene glycol after inhalation exposure were found in the literature.

2.3.1.2 Oral Exposure

Since human exposure to ethylene glycol is usually oral by accidental means, or intentional ingestion without records of the amount ingested, data describing absorption of ethylene glycol after human oral exposure were not found in the literature.

In rats, ingested ethylene glycol is rapidly absorbed and evenly distributed throughout the body reaching peak blood levels l-4 hours after ingestion of doses of 7-29 mg/kg (Winek et al. 1978). Recovery of ethylene glycol after oral exposure of rats and mice to doses up to 1,000 mg/kg is approximately 90-100%, indicating substantial absorption (Frantz et al. 1989, 1991). Serum levels of ethylene glycol in dogs suspected to have ethylene glycol intoxication from oral exposure were 0.148-4.080 g/dL (Dial et al. 1989). When Dial et al. (1994) conducted a controlled study of ethylene glycol toxicity in dogs after oral administration, semm blood levels of ethylene glycol were determined in animals receiving 4-methyl pyrazole, an alcohol dehydrogenase inhibitor, 5 or 8 hours after ingestion of 10,070-10,600 mg/kg ethylene glycol. Serum concentration peaked 6 hours after exposure in both treatment groups. Peak level were approximately 900 mg/dL in dogs treated 5 hours after ethylene glycol ingestion, and 800 mg/dL in dogs treated 8 hours after ethylene glycol ingestion.

The pharmacokinetic properties of propylene glycol are not completely understood, but absorption from the gastrointestinal tract is fairly rapid. The maximum plasma concentration of propylene glycol in humans is reached within 1 hour after oral exposure (Yu et al. 1985). An equal number (5-6) of cats of both sexes were fed a diet containing 12% propylene glycol (low dose, 1,600 mg/kg/day) for

5 weeks, a dose equivalent to that found in commercial soft-moist cat foods, or a high dose diet containing 41% propylene glycol (8,000 mg/kg/day) for 22 days (Christopher et al. 1990b). Predosing observations were made such that each group of cats served as its own control. Plasma levels of propylene glycol were measured in 2 cats fed the low dose on day 24 of ingestion, and compared to pre-dosing samples. Plasma levels of propylene glycol were 19.1 and 8.4 mmol/liter for the 2 cats.

2.3.1.3 Dermal Exposure

Since human exposure to ethylene glycol is often dermal by accidental means, without records of the amount, data describing absorption of ethylene glycol after *in vivo* human exposure were not found in the literature. The in vitro permeability of human skin to ethylene glycol was determined by Loden (1986). The rate of resorption was 118 μg/cm^2/hour, with a steady state concentration of 0.97 mg/cm^2. Additional *in vitro* studies of dermal absorption of ethylene glycol have been conducted. The percutaneous absorption of [^{14}C]ethylene glycol through human skin was evaluated (Driver et al. 1993). Radiolabeled ethylene glycol was applied to the surface of three different fresh human skin samples at a dose of 8 μg/cm^2. After 24 hours of exposure, 18.3% of the applied dose was recovered from the receptor fluid (absorbed through the skin), 8.3% in the skin, and 12.5% in the skin surface, for a total of approximately 39% recovery of the applied dose. Individual differences existed for the three samples; average potential absorption was 26.6%. This represented an absorption rate of approximately 0.09 μg/cm^2/hour for ethylene glycol.

In dermal applications using an occlusion bandage, approximately 30% of doses of ethylene glycol up to 1,000 mg/kg was absorbed through rat skin (Frantz et al. 1989), whereas mice absorbed 85-100% of the administered dose (Frantz et al. 1991). Thus, some species differences exist in the permeability of animal skin to this chemical.

Some studies of the dermal absorption of propylene glycol have been conducted. Patients with second and third degree bums over more than 20% of their total body surface were studied over a period of 30 months (Kulick et al. 1985). Sulfadiazine preparations containing propylene glycol were applied dermally over a period of 3-7 days after admission to the hospital. Serum and urinary levels of propylene glycol were measured. Propylene glycol was detected in the serum of 24 of 45 patients, and in the urine of 40 of 45 patients. Average serum levels were 0.08 mg/mL, with a range of 0-1.3 mg/mL for patient who lived, and 0.82 mg/mL with a range of 0-9.8 mg/mL for patients who

died. Propylene glycol levels correlated with total bum surface area and total third degree bum surface area.

In vitro studies of the penetration of propylene glycol through rat abdominal stratum comeum have been conducted (Takeuchi et al. 1993, 1995). Fresh abdominal skin from male Wistar rats was used in experiments in which propylene glycol, or a mixture of propylene glycol and oleic acid were evaluated for absorption properties (Takeuchi et al. 1993). When propylene glycol was applied alone for up to 2 hours, no compound was detected in the dermis. However, when 0.15 M oleic acid was added to the propylene glycol, propylene glycol was detected in the dermis after 30 minutes of exposure, but not after 5 or 15 minutes (Takeuchi et al. 1993). The appearance of propylene glycol seemed to be in three phases when in the presence of a skin penetration enhancer such as oleic acid (Takeuchi et al. 1995). The first stage was the penetration of propylene glycol into the skin barrier, without any change of the dermal structure. The second stage was rapid distribution in and throughout the dermis, presumably accompanied by alteration of the dermal structure. In the third stage, propylene glycol was saturated in the dermis.

Comparison of propylene glycol absorption by skin from humans, hairless mice, and snakes was conducted (Rigg and Barry 1990). Shed snake skin tended to underestimate propylene glycol absorption in human skin, especially in the presence of enhancers, whereas hairless mouse skiu greatly overestimated absorption compared to human skin. The authors concluded that human skin should be used for absorption studies whenever possible.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No kinetic data for distribution in humans or animals of ethylene glycol or propylene glycol after inhalation exposure were found in the literature.

2.3.2.2 Oral Exposure

The apparent volume of distribution of ethylene glycol has been determined by calculation from clearance data in two patients, to be 0.54 and 0.56 L/kg (Jacobsen et al. 1988). Also, the urine to

plasma concentration ratios for several ethylene glycol determinations in one patient were about 1.0-1.4, similar to those of ethanol. These data suggest a total body water distribution for ethylene glycol.

In rats, 10-20% of oral doses up to 1,000 mg/kg of ethylene glycol were recovered from the body tissues and carcass 96 hours after a single dose (Frantz et al. 1989), whereas mice retained only a small percentage of the dose in their tissues (Frantz et al. 1991).

No studies of the distribution of propylene glycol in humans or animals after oral exposure were found in the literature.

2.3.2.3 Dermal Exposure

Distribution of a 100 or 1,000 mg/kg cutaneous undiluted dose of radiolabled ethylene glycol or a 1,000 mg/kg dose of a 50% aqueous solution of ethylene glycol using an occlusive bandage was determined in mice (Frantz et al. 1991). At 100 mg/kg undiluted ethylene glycol, 99.5% of the dose was recovered, with tissues and excreta accounting for 76.5%. Most was recovered as volatile organic radioactivity (2-S39%) or as radioactive CO_2 (8-12%). Urine and feces each accounted for another 4-9% of the dose. Tissue recoveries were less than 1% of the dose, while the residual carcass contained about 10-18% of the dose. Cage wash water and the bandage itself accounted for the rest of the dose. Following the 1,000 mg/kg undiluted ethylene glycol application, total recovery was 89% of the dose: 84% in tissues and excreta, and approximately 7% in feces, cage wash water, and carcass. Recovery from the 1,000 mg/kg dose in 50% aqueous solution was similar to the undiluted dose. Tissue recoveries for all three doses were similar, with the liver showing the highest level (0.58-0.59%), followed by the kidney (0.06-0.07%), the brain and lung (0.02-0.03% each), the REKs (0.009-0.014), plasma (0.008-0.009%), and fat (0.005-0.008%).

In vitro studies of the penetration of propylene glycol through rat abdominal stratum corneum have been conducted (Takeuchi et al. 1993, 1995). Fresh abdominal skin from male Wistar rats was used in experiments in which propylene glycol, or a mixture of propylene glycol and oleic acid were evaluated for absorption properties (Takeuchi et al. 1993). When propylene glycol was applied alone for up to 2 hours, no compound was detected in the dermis. However, when 0.15 M oleic acid was added to the propylene glycol, propylene glycol was detected in the dermis after 30 minutes of exposure, but

not after 5 or 15 minutes (Takeuchi et al. 1993). The appearance of propylene glycol seemed to be in three phases when in the presence of a skin penetration enhancer such as oleic acid (Takeuchi et al. 1995). The first stage was the penetration of propylene glycol into the skin barrier, without any change of the dermal structure. The second stage was rapid distribution in and throughout the dermis, presumably accompanied by alteration of the dermal structure. In the third stage, propylene glycol was saturated in the dermis. Additional evaluation indicated that the volume of distribution of propylene glycol in the dermis was influenced by the efficiency of the enhancer compound, with oleic acid and oleylamine being the most efficient, compared to lauric acid, laurylamine, or azone.

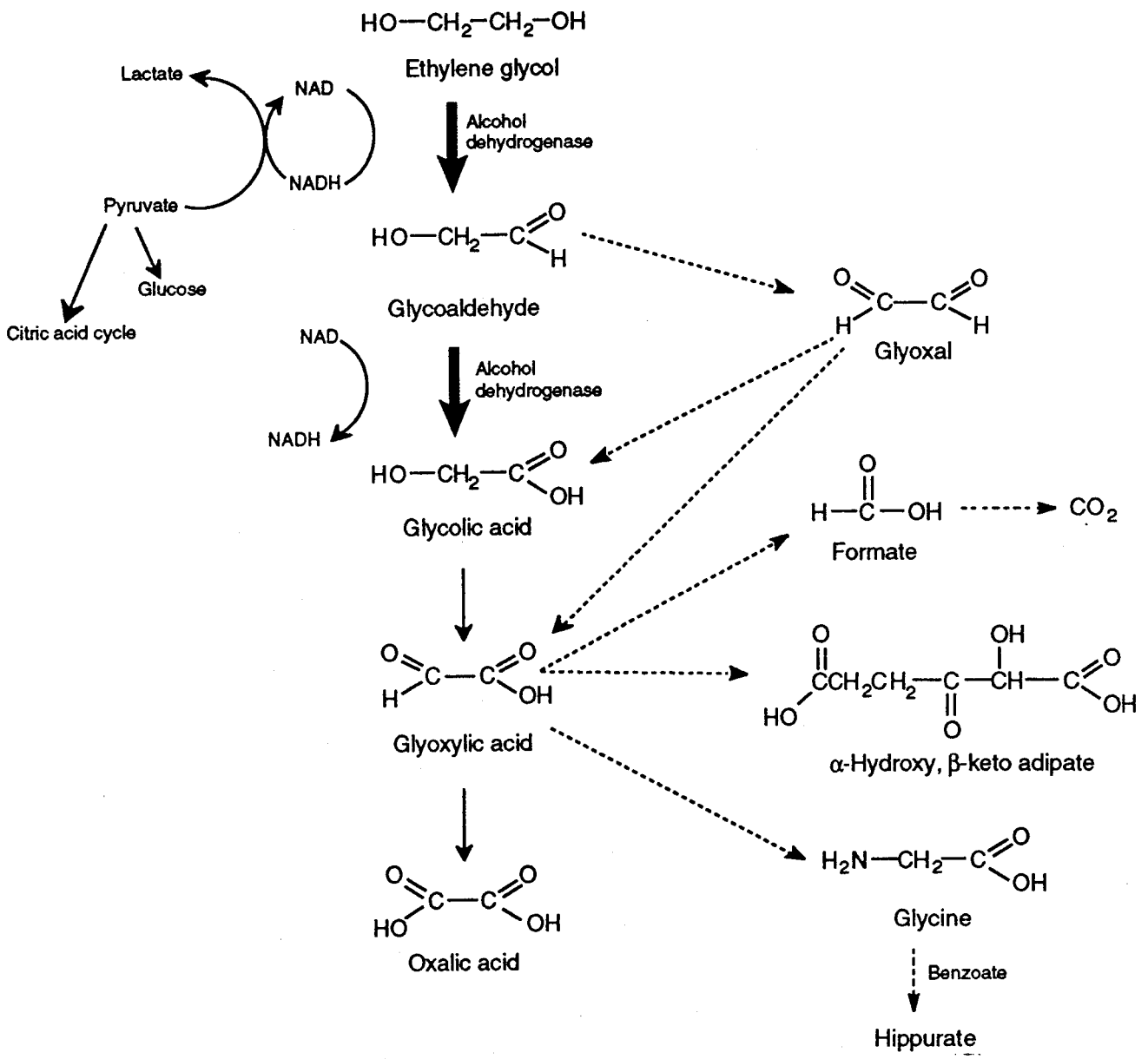
2.3.3 Metabolism

The metabolic pathway for ethylene glycol is shown in Figure 2-5. Solid arrows in Figure 2-5 represent the steps that are quantitatively most important while the broken arrows indicate minor metabolic conversions in humans. Knowledge of ethylene glycol metabolism helps one understand its mechanism of action, the pathogenesis of its toxicity, and the rationale for treatment of acute ethylene glycol intoxication. This knowledge comes from studies investigating oxidative biodegradation of ethylene glycol. Ethylene glycol is oxidized to glycolaldehyde by nicotinamide adenine dinucleotide (NAD)-dependent alcohol dehydrogenase in the liver and kidney. Glycolaldehyde is further oxidized to glycolic acid by mitochondrial aldehyde dehydrogenase and cytosolic aldehyde oxidase; glycolic acid is oxidized to glyoxylic acid by glycolic acid oxidase or lactic dehydrogenase. The enzyme catalyzing the formation of oxalic acid from glyoxylic acid is glycolic acid oxidase. Glyoxylate can induce lactic acid formation via oxalomalate production and its inhibitory effects on the citric acid cycle (Gabow et al. 1986; Jacobsen et al. 1988; Parry and Wallach 1974; Robinson and McCoy 1989; Vale 1979; Wiener and Richardson 1988).

The levels of plasma glycolate were determined in 3 cases (2 female infants and 1 adult male) of accidental ethylene glycol intoxication (Hewlett et al. 1986). Plasma levels of glycolate ranged from 12.2-15.4 mmol/L. The infants survived, and the adult male died, probably due to delayed treatment for metabolic acidosis. In another study with 6 patients, one of whom died, plasma glycolate levels on admission ranged from 17.0-29.3 mmol/L (Jacobsen et al. 1984)

In rats given 200 mg/kg ethylene glycol by gavage, peak plasma levels of ethylene glycol occurred 2 hours after administration, while plasma glycolate levels peaked 4 hours after dosing (Hewlett et al.

Figure 2-5. Metabolic Pathway for Oxidation of Ethylene Glycol



Adapted from Gabow et al. 1986; Jacobsen et al. 1988; Robinson and McCoy 1989; Vale 1979; Wiener and Richardson 1988.

1989). Dogs receiving 100 or 136 mg/kg ethylene glycol by gavage exhibited peak ethylene glycol levels at 2 hours after dosing (Hewlett et al. 1989). Male Porton rats receiving 999-1,110 mg/kg ethylene glycol in the drinking water for 21 days exhibited urinary oxalate levels equivalent to 1.18% conversion of ethylene glycol to oxalate; rats given diets supplemented with 30% or 60% sucrose excreted oxalate equivalent to 1.11 and 0.7% conversion of ethylene glycol, respectively (Rofe et al. 1986).

The metabolic pathway for propylene glycol in mammals is shown in Figure 2-6. Commercially available propylene glycol is usually a mixture of D- and L-isomers. The major route of metabolism for propylene glycol is via alcohol dehydrogenase to lactaldehyde, then to lactate, via aldehyde dehydrogenase, and on to glucose through gluconeogenic pathways (as summarized in Christopher et al. 1990b; Huff 1961; Miller and Bazzano 1965; Morshed et al. 1989, 1991b; Ruddick 1972). Conversion to methylglyoxal is an alternate route via alcohol dehydrogenase, ending in metabolism to D-lactate through glyoxalase.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

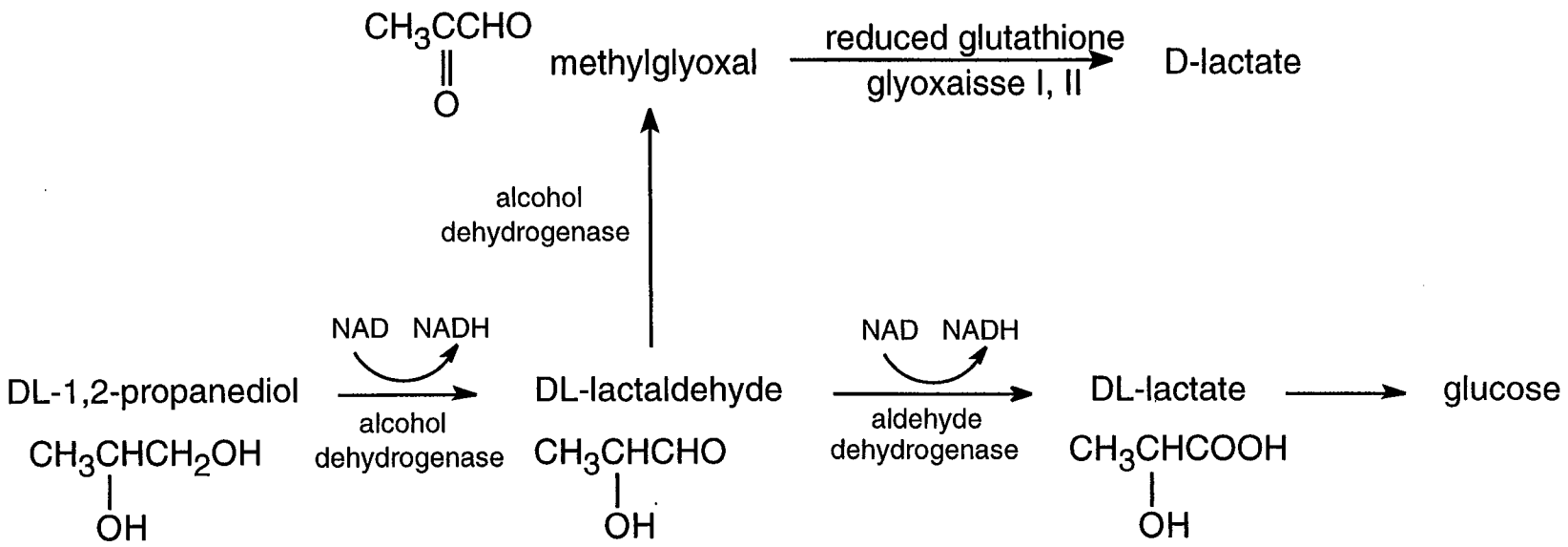
No kinetic data for excretion in humans or animals of ethylene glycol or propylene glycol after inhalation exposure were found in the literature.

2.3.4.2 Oral Exposure

Approximately 24-48 hours after ethylene glycol ingestion, it is difficult to detect ethylene glycol in either urine or tissues (Winek et al. 1978); this supports its relatively rapid biotransformation. The approximate serum half-life of ethylene glycol is 2.5 hours for children (Rothman et al. 1986), and 2.7 hours for adults during hemodialysis (Cheng et al. 1987). In untreated adults, the serum half-life has been estimated to be between 3.0 and 8.4 hours (Jacobsen et al. 1988; Peterson et al. 1981).

The elimination half-life for ethylene glycol in the plasma has been estimated at 1.7 and 3.5 hours in rats and dogs given 2,000 mg/kg and l,000-1,360 mg/kg, respectively; 1.4-2.5 hours in rats given 10-1,000 mg/kg; and 0.3-1.1 hours in CD-l mice given 10-1,000 mg/kg (Frantz et al. 1989, 1991;

Figure 2-6. Propylene Glycol Metabolism in Mammals



From Christopher et al. 1980b

Hewlett et al. 1989). All kinetic parameters were determined in the terminal phase of elimination after oral dosing. Data from intravenous administration of ethylene glycol show similar elimination halflives (Frank et al. 1989, 1991; Martis et al. 1982).

In rats given oral doses of radioactive ethylene glycol up to 1,000 mgkg, the major excretory route of ^{14}C was via CO_2 exhalation (42%), while 24% of the dose was excreted via the urine and 3% via the feces (Frantz et al. 1989). Mice showed a similar profile, exhaling 55% of the dose, and excreting 24% in the urine and up to 12% in the feces (Frantz et al. 1991). The majority of the exhaled radioactivity was eliminated during the first 12 hours after dosing (Frantz et al. 1989, 1991). In contrast, approximately 50% of an oral dose of ethylene glycol administered to dogs was excreted via the urine (Grauer et al. 1987).

When Dial et al. (1994) conducted a controlled study of ethylene glycol toxicity in dogs after oral administration, serum half-life of ethylene glycol was determined in animals receiving 4-methyl pyrazole, an alcohol dehydrogenase inhibitor, 5 or 8 hours after ingestion of 10,070-10,600 mg/kg ethylene glycol. The half-life was 7 hours in dogs treated 5 hours after ethylene glycol ingestion, and 15 hours in dogs treated 8 hours after ethylene glycol ingestion. Urine concentration peaked 3 hours after ethylene glycol ingestion in dogs treated after 5 hours, and at 9 hours in dogs treated 8 hours after exposure. The percentage of ethylene glycol excreted unchanged was significantly greater in dogs treated 5 hours after ingestion, compared to dogs treated 8 hours after ingestion.

The pharmacokinetic properties of propylene glycol are not completely understood, but absorption from the gastrointestinal tract is fairly rapid. The maximum plasma concentration of propylene glycol in humans is reached within 1 hour after oral exposure, while the elimination half-life is about, 4 hours. The total body clearance is about 0.1 L/kg/hour and seems to be serum-concentration dependent (Yu et al. 1985). Dose-dependent elimination is seen in rats, with saturation of the pathways at doses above 5,880 mg/kg (Morshed et al. 1988). An apparent maximum elimination rate of 8.3 mmol/kg/hour (630 mg/kg/hour) was observed.

2.3.4.3 Dermal Exposure

After dermal application of ethylene glycol, rats absorbed only 31% of doses up to 1,000 mg/kg, 14% of the absorbed dose was expired, while 7% was excreted in the urine, and 1% was recovered from the

feces (Frantz et al. 1989). Distribution of a 100 or 1,000 mg/kg cutaneous undiluted dose of radiolabled ethylene glycol or a 1,000 mg/kg dose of a 50% aqueous solution of ethylene glycol using an occlusive bandage was determined in mice (Frantz et al. 1991). At 100 mg/kg undiluted ethylene glycol, 99.5% of the dose was recovered, with tissues and excreta accounting for 76.5%. Most was recovered as volatile organic radioactivity (25-39%) or as radioactive CO_2 (8-12%). Urine and feces each accounted for another 4-9% of the dose. Tissue recoveries were less than 1% of the dose, while the residual carcass contained about 10-18% of the dose. Cage wash water and the bandage itself accounted for the rest of the dose. Following the 1,000 mgkg undiluted ethylene glycol application, total recover was 89% of the dose: 84% in tissues and excreta, and approximately 7% in feces, cage wash water, and carcass. Recovery from the 1,000 mgkg dose in 50% aqueous solution was similar to the undiluted dose.

Excretion of propylene glycol has been studied in humans. Patients with second and third degree bums over more than 20% of their total body surface were studied over a period of 30 months (Kulick et al. 1985). Sulfadiazine preparations containing propylene glycol were applied dermally over a period of 3-7 days after admission to the hospital. Serum and urinary levels of propylene glycol were measured. Propylene glycol was detected in the serum of 24 of 45 patients, and in the urine of 40 of 45 patients. Average urinary levels were 1.3 mg/rnL, with a range of 0-17.9 mg/mL for patient who lived, and 2.9 mg/mL with a range of 0-23.0 mg/mL for patients who died. Propylene glycol levels correlated with total bum surface area and total third degree bum surface area.

2.3.5 Mechanism of Action

The mechanism of action of ethylene glycol can be best explained by describing the main effects that follow its ingestion: increased osmolal gap, metabolic acidosis, and formation of calcium oxa.late crystals. The elucidation of ethylene glycol metabolism (Figure 2-5) has helped in the understanding of its mechanism of toxic action.

In the initial stages after ingestion of ethylene glycol, its concentration in extracellular fluids increases, leading to increased osmolality. This increased osmolality (hyperosmolarity) further leads to an increased osmolal gap, one of the hallmarks of ethylene glycol intoxication. Osmolal gap is defined as a difference between the measured and calculated osmolality. Osmolality (calculated) can be estimated from the formula that takes into account normal serum concentrations of sodium, glucose, and BUN.

This calculated osmolality is then compared to the serum osmolality measured following ethylene glycol ingestion; a difference greater than 10 indicates an increased osmolal gap (Fligner et al. 1985). The increased osmolal gap is not solely characteristic of ethylene glycol intoxication and can occur when any osmotically active, non-measured solute (e.g., mannitol) is present in the serum. In dogs given oral doses of 10,743 mg/kg ethylene glycol, serum osmolality peaked (460 milliosmoles/kg) at 3-6 hours, and the osmolal gap peaked (134 milliosmoles/kg) at 3 hours, coinciding with peak serum ethylene glycol levels at 3 hours (Grauer et al. 1984). In these animals, the anion gap was also significantly increased at 3 hours (19 Meq/L).

The second characteristic of ethylene glycol intoxication is metabolic acidosis. Ethylene glycol itself has low toxicity (Godolphin et al. 1980; Jacobsen and McMartin 1986), but it is metabolized to a variety of toxic metabolites such as glycolaldehyde, glycolic acid (glycolate), glyoxylic acid (glyoxylate), and oxalic acid (oxalate) (Jacobsen et al. 1988; Parry and Wallach 1974; Vale 1979; Wiener and Richardson 1988). In general, the accumulation of acids leads to acidosis, a state that is characterized by actual or relative decrease of alkali in body fluids in relation to the acid content. In the case of ethylene glycol, metabolic processes that follow ethylene glycol ingestion lead to the accumulation of glycolic and lactic acids resulting in metabolic acidosis. The assumption that ethylene glycol toxicity is due to its metabolic products is made because there is a latent period before the symptoms of acidosis appear, because there is no correlation between observed toxicity and ethylene glycol blood concentration, and because inhibition of ethylene glycol oxidation prevents toxicity (Jacobsen and McMartin 1986). Furthermore, glycolic acid is the most abundant of all ethylene glycol metabolites (Jacobsen et al. 1984). Following ingestion of high doses of ethylene glycol, glycolic acid tends to accumulate because it is a substrate for lactic dehydrogenase and/or glycolic acid oxidase.

The accumulation of metabolites such as glycolic acid, oxalate, and lactic acid leads to an increased anion gap and metabolic acidosis, which are responsible for toxicity observed after ethylene glycol ingestion. While lactate levels increase in some human cases up to 5-7 mmol (Jacobsen et al. 1984, 1988; Parry and Wallach 1974), glycolate levels range up to 20-25 mmol, thus accountiiig for a greater portion of the anion gap. The serum anion gap is calculated by subtracting the sum of the serum chloride and bicarbonate ions from serum sodium ions. In dogs given oral doses of 10,743 mg/kg ethylene glycol, the anion gap was significantly increased at 3 hours (19 Meq/L) coinciding with peak serum ethylene glycol levels (Grauer et al. 1984). The maximum production of metabolites occurs 6-12 hours after ethylene glycol ingestion and coincides with neurotoxicity.

Ethylene glycol metabolites inhibit oxidative phosphorylation, respiration, glucose metabolism, protein synthesis, deoxyribonucleic acid (DNA) replication, ribosomal ribonucleic acid (RNA) synthesis, central nervous system respiration, and serotonin metabolism (Vale 1979). Glycolic acid and lactic acid are the major and minor contributors, respectively, to the production of metabolic acidosis, one of the hallmarks of acute ethylene glycol intoxication.

Nephrotoxicity and neurotoxicity can follow because oxalate can produce renal and brain damage as it chelates with calcium ions forming insoluble calcium oxalate. monohydrate crystals, another characteristic of ethylene glycol poisoning (Jacobsen et al. 1988). This may lead to hypocalcemia and imbalance of serum divalent ion concentrations (Zeiss et al. 1989). Although the mechanism of ethylene glycol neurotoxicity is not completely understood, the available information on humans suggests that it occurs in two stages, an early one (30 minutes to 12 hours after exposure) and a late one (several days after exposure). The early-stage symptoms are due to the direct toxicity of ethylene glycol, while the late-stage neurotoxicity is due to metabolic acidosis caused by the accumulation of ethylene glycol metabolites, primarily glycolic acid, which leads to metabolic acidosis. Additional evidence for this late neurotoxicity is crystalline deposits of calcium oxalate in the walls of small blood vessels found in the brain of a man who died of acute ethylene glycol poisoning (Zeiss et al. 1989). Similar effects were observed in rats fed 2,500 mg/kg/day ethylene' glycol for 13 weeks (Melnick 1984). The role of calcium in ethylene-glycol-induced neurotoxicity is not known but the formation of calcium oxalate crystals may cause perturbation of intracellular calcium homeostasis causing membrane abnormalities generally associated with cell injury and cell death.

The presented data indicate that glycolic acid is the major toxic metabolite contributing to metabolic acidosis, which is a primary cause of systemic toxicity following exposure to ethylene glycol.

The mechanism of action of propylene glycol is not well understood.

2.4 RELEVANCE TO PUBLIC HEALTH

Ethylene glycol is a chemical that is common in many consumer products, including antifreeze, de-icing solutions, printer's ink, stamp pads, and ballpoint pen ink. It is widely sold in grocery, hardware, and home supply stores. In addition, it is used for de-icing airplanes and other machinery; generation of artificial smokes, mists, and fogs; and in the manufacture of polyester fibers, and various

paints and coatings. By far, the most common route of exposure to ethylene glycol is dermal, through the process of changing the antifreeze in an automobile. However, most of the human toxicity data has been derived from accidental or intentional ingestion of ethylene glycol. There are often three stages of oral ethylene glycol toxicity in humans. They are well documented and occur within 72 hours after ingestion (Robinson and McCoy 1989; Vale 1979). The first stage involves central nervous system depression, metabolic changes (hyperosmolality and acidosis), and gastrointestinal upset, and spans the period from 30 minutes to 12 hours. During the second stage of ethylene glycol toxicity (12-24 hours after ingestion), cardiopulmonary symptoms (tachypnea, hyperpnea, and tachycardia) become evident. These symptoms are largely due to metabolic acidosis. During stage three, which covers the period 24-72 hours after ethylene glycol ingestion, renal involvement becomes evident. The third stage is characterized by flank pain and oliguria/anuria. The histopathological findings show renal tubular necrosis and deposition of calcium oxalate crystals (Vale 1979). Often the cardiopulmonary effects in the second stage are not evident, so the distinguishing symptoms of ethylene glycol intoxication are central nervous system depression, acidosis, and nephrotoxicity (Jacobsen and McMartin 1986; Karlson-Stilber and Persson 1992). One study defines a fourth stage as the late cerebral stage that occurs 6-13 days after ethylene glycol ingestion (Chung and Tuso 1989). Animal studies include exposure by inhalation, oral and dermal routes. Many of the same toxic events that have been identified in humans after oral exposure have been identified in animals as well.

Propylene glycol is a colorless, odorless, water-soluble liquid considered safe for use in commercial formulations of foods, drugs, and cosmetics. Propylene glycol, like ethylene glycol, is used as an antifreeze, de-icing solution, and in various paints and coatings. Unlike ethylene glycol, however, propylene glycol has been approved as safe in various food flavorings, drugs, cosmetics, and as a direct additive to food. Propylene glycol is commonly used in the pharmaceutical industry as a solvent for drugs, as a stabilizer for vitamins, and in ointment for medicinal applications. Propylene glycol may be found in canned fruit, packaged coconut, as a solvent in drug and cosmetic preparations, and in flavorings and extracts. Propylene glycol is also used in the generation of artificial mists and fogs used in fire safety training, and theatrical and stage productions: This widespread use of propylene glycol stems from its low level of toxicity.

Minimal Risk Levels for Ethylene Glycol

Inhalation MRLS

- An MRL of 0.5 ppm has been derived for acute-duration inhalation exposure (14 days or less) to ethylene glycol.

The MRL was based on a NOAEL of 197 ppm for increased renal weight (Tyl 1988a). The MRL was obtained by dividing the NOAEL value by 100 (10 for extrapolation from animals to humans, and 10 for human variability) and adjusting for the intermittent exposure (6/24 hours). Timed-pregnant CD-l mice were exposed to ethylene glycol aerosol on Gd 6-15, 6 hours per day by nose-only procedures at doses of 0, 500, 1,000, or 2,500 mg/m3 (0, 197, 394, or 985 ppm) target concentration (Tyl 1988a). Control animals were exposed to water aerosol (4,200 mg/m^3 or 5,705 ppm). Females were weighed, observed daily for clinical signs, and evaluated for water consumption. At termination on Gd 18, females were evaluated for body weight, gravid uterine weight, liver weight, and kidney weight. Ovarian corpora lutea were counted and all uterine implantation sites evaluated. Maternal body weight was unaffected. No dose-related clinical signs were noted. Water consumption was not significantly affected. At termination, liver weight was not affected. Absolute maternal kidney weight was increased at 394 and 985 ppm and relative maternal kidney weight was increased at 985 ppm, but no treatment-related lesions were observed. In this regard, metabolic acidosis and renal toxicity are the hallmarks of ethylene glycol toxicity. Both these effects arise from the metabolism of ethylene glycol to glycolic acid (acidosis) and oxalate (oxalate nephrosis). Frank renal toxicity from ethylene glycol is usually accompanied by the observation of oxalate crystals in the renal tissue and in the urine. In the Tyl (1988a) study, oxalate nephrosis was not observed. However, increased kidney weight has been observed in conjunction with oxalate nephrosis in other studies after oral exposure to ethylene glycol (DePass et al. 1986a; Woodside 1982). Since the increase in kidney weight showed a dose-response relationship and was detected in the absolute kidney weight at the mid dose, but at both absolute and relative kidney weight at the high dose, it may be assumed that the increase in kidney weight observed is related to renal toxicity. In addition, the developmental evaluation of the offspring from this study indicate a NOAEL at the mid dose and reduced fetal body weight and increased incidence of skeletal variations at the high dose. Developmental effects from ethylene glycol appear to be the result of maternal metabolic acidosis (Khera 1991). It appears that in the mouse, the maternal kidney was the most sensitive indicator of those parameters evaluated. Of the available acute inhalation studies, Tyl (1988a) had the highest NOAEL that was associated with a dose-related effect.

It is notable that the LOAEL for maternal toxicity in this study is equal to the NOAEL for developmental toxicity in this study. Effects observed in humans suggest a similar MRL. For instance, in a study by Wills et al. (1974), male volunteers experienced upper respiratory tract irritation after a 1.5minute exposure to ethylene glycol in ambient air at 55 ppm; doses above 79 ppm were not tolerated.

MRLs for intermediate-duration (15-364 days) and chronic-duration inhalation exposure (2365 days) have not been derived because suitable NOAELs or LOAELs have not been identified in the available literature. The intermediate-duration exposure inhalation study (Wills et al. 1974) did not provide enough detail on the exact exposure regimen to associate effects with concentrationsof ethylene glycol. Neither of the two chronic-duration inhalation studies (Bond et al. 1985; Triosi 1950) provided measured concentrations of exposure.

Oral MRLs

- An MRL of 2.0 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to ethylene glycol.

The MRL was based on a NOAEL of 150 mg/kg/day for developmental toxicity in mice (Tyl 1989). The MRL was obtained by dividing the NOAEL value by 100 (10 for extrapolation from animals to humans, and 10 for human variability). Timed-pregnant CD-l mice were given ethylene glycol by gavage on Gd 6-15. Females were weighed, observed daily for clinical signs, and evaluated for water intake. At sacrifice on Gd 18, females were evaluated for body weight, gravid uterine weight, liver weight, and kidney weight. Kidneys from control and high dose dams were examined microscopically. Uterine contents were evaluated. There were no significant effects on the number of corpora lutes/dam, the number of total, nonviable, or viable implants/litter, or on sex ratio. Fetal body weights per litter were reduced only at 1,500 mg/kg/day. There was no increase in the incidence of individual or total external or visceral malformations in any group relative to the vehicle control. There was a significant increase in the incidence of two skeletal malformations (fused ribs or thora& arches) in the 1,500 mg/kg/day group, and the incidences of pooled skeletal malformations and all malformations were significantly increased in this group as well. The incidence of total malformations per litter was also significantly increased at 500 mg/kg/day. There were no significant increases in individual external or visceral variations, or in pooled external, visceral or skeletal variations or in total variations. The incidences of 23 skeletal variations were increased in the 1,500 mg/kg/day group.

One skeletal variation (bilateral extra rib 14) was also increased at 500 mg/kg/day. Other developmental studies have identified ethylene glycol as a developmental toxicant after oral administration in animals, which adversely affects the conceptus at levels that do not cause significant adverse effects in the maternal animal. In the cited study (Tyl 1989), the maternal NOAEL is 1,500 mg/kg/day, compared to a developmental NOAEL of 150 mg/kg/day. In mice, 750 mg/kg/day caused reduced litter size and increased incidence of skeletal malformations, but was a maternal NOAEL (Price et al. 1985). Neeper-Bradley (1990) detected an increase in skeletal malformations in rats treated orally with 1,000 mg/kg/day ethylene glycol on Gd 6-15, with a NOAEL for developmental effects of 500 mg/kg/day. The maternal NOAEL in that study was 2,500 mg/kg/day. Similarly, Price et al. (1985) determined a developmental LOAEL of 1,250 mg/kg/day (skeletal malformations) in rats treated orally during gestation, a dose that caused only a 17% decrease in body weight in the maternal dams. Thus, using oral exposure during the period of major organogenesis in the rodent (Gd 6-15), the developmental effects are the most sensitive end point.

An MRL for intermediate-duration oral exposure has not been derived because a suitable LOAEL or LOAEL value has not been identified in the available literature.

Intermediate-duration oral studies have found increased kidney weight and oxalate nephrosis in rats fel 1,250 and 2,500 mg/kg/day ethylene glycol, but not 625 mg/kg/day ethylene glycol for 13 weeks (Melnick 1984). In a reproductive study, decreased prenatal and postnatal viability was observed in female inice treated with 2,500 mg/kg/day ethylene glycol for 20 days and mated to male mice dosed with the same treatment level (Harris et al. 1992). No effects were seen at 700 mg/kg/day. Although either of these studies might be appropriate to use for the derivation of the MRL, the resultant value would be higher than the acute-duration oral MRL.

- An MRL of 2.0 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to ethylene glycol.

The MRL was based on a NOAEL 200 mg/kg/day for renal toxicity in rats (DePass et al. 1986a; Woodside 1982). The MRL was obtained by dividing the NOAEL value by 100 (10 for extrapolation from animals to humans and 10 for human variability). Groups of 130 male and female rats were fed diets to achieve dosage goals of 0, 40, 200, or 1,000 mg/kg/day ethylene glycol for 24 months. Mortality, body weight, diet consumption, histopathological findings, and gross findings were monitored. No evidence of oncogenicity was found. High-dose males (1,000 mg/kg/day) died prior to

the 18-month termination, with death attributable to oxalate nephrosis caused by ethylene glycol exposure. Calcium oxalate crystals were found in the urine of high-dose males and females at 12 months. Increased absolute and relative kidney weights were observed only in high-dose males at 12 months. At 12 months, high-dose males had chronic nephritis (including tubular dilation, and proteinosis, glomerular shrinkage, tubular cell hyperplasia, and chronic interstitial nephritis). These results were supported by hematological effects also reported in the same study. Males in the highdose group had decreases in RBC count, hematocrit, hemoglobin, and increases in neutrophils at 12 months. No effects were seen at the loier doses. Females had normal hematology. Males in the high-dose group had a 4-fold increase in BUN and creatinine at 12 months, but no changes were noted at lower dose levels. At 12 months, high-dose males showed increases in urine volume, and a reduction in urine specific gravity. The only change seen in the urinalysis of females at 12 months was a reduction in mean pH at the high-dose level. High-dose males exhibited a significant reduction in absolute and relative liver weight at 12 months. High-dose females, but not males, had mild fatty metamorphosis of the liver; organ weight was normal. Females had normal body weight gain; highdose males had decreased weight gain at 12 months of treatment. Mineralization, but no other lesions and no other organ weight changes, were seen in heart, lungs, and stomach in males, but not in females.

Other studies report similar effects. In NTP 1982, male B6C3F, mice exhibited oxalate nephrosis at 3,315 mg/kg/day, degeneration of the centrilobular hepatocytes at 1,625 mg/kg/day, and a NOAEL for hepatic effects of 812.5 mg/kg/day ethylene glycol for 2 years. In the same study, females showed hepatic and pulmonary effects at 6,500 mg/kg/day, with a NOAEL of 3,250 mg/kg/day. DePass et al. (1986a) indicates a NOAEL of 1,000 mg/kg/day for renal effects in CD-l mice after a 2-year exposure to ethylene glycol in the feed.

The EPA (IRIS 1995) assigned ethylene glycol a reference dose (RfD) of 2.0 mg/kg/day with an uncertainty factor of 100 based on a NOAEL of 200 mg/kg/day kidney toxicity in rats (DePass et al. 1986a). The chronic-duration MRL developed by the Agency for Toxic Substances and .Disease Registry for ethylene glycol is not in conflict with the current RfD for ethylene glycol.
Death.There were no reports of death from inhalation or dermal contact with ethylene glycol. Thus, contact with ethylene glycol through changing the antifreeze in an automobile, inhaling vapors from de-icing solutions, or the use of ink, paints, or other coatings is not likely to carry a significant risk of fatality. Death from ethylene glycol exposure is associated with the accidental and (more often)

intentional ingestion of ethylene glycol. The amount of ethylene glycol that can be ,accidentally ingested through normal activities (e.g., putting your fingers in your mouth, tasting an unknown liquid) is not likely to cause any adverse effects. Reports of fatalities following ingestion of ethylene glycol indicate that a volume of 150-1,500 mL (3/4-6 cups) consumed at one time may be necessary to cause death (Walton 1978). Because ethylene glycol ingestion is a common source of poisoning in domestic animals, information on fatalities in companion animals is important. Dogs and cats receiving approximately 4,000 mg/kg ethylene glycol exhibited loss of reflexes, central nervous system depression, and coma prior to death (Beckett and Shields 1971; Kersting and Nielson 1965; Penumarthy and Oehme 1975). In laboratory animals (rats, mice, monkeys) receiving a single oral dose, similar to the.scenario of an accidental or intentional ingestion of a large amount, doses in the range of 4,000 mg/kg and greater were needed to cause death (Clark et al. 1979; Richardson 1973). Administration for longer periods of time at lower doses also caused death (Blood 1965; DePass et al. 1986a; Schuler et al. 1984; Tyl et al. 1993; Woodside 1982). Monkeys given 4,000 mg/kg ethylene glycol intraperitoneally also exhibited lethal toxicity (Clay and Murphy 1977).

Systemic Effects.

Respiratory Effects. Respiratory effects occur 12-24 hours after ingestion of large amounts of ethylene glycol, and are considered to be a second stage of ethylene glycol poisoning (Vale 1979). The symptoms include hyperventilation (Godolphin et al. 1980; Gordon and Hunter 1982), shallow rapid breathing (Woolf et al. 1992; Zeiss et al. 1989) and generalized pulmonary edema with calcium oxalate crystals occasionally present in the lung parenchyma (Vale 1979). Throat and upper respiratory tract irritation was observed after inhalation exposure to 12 ppm for 20-22 hours per day for 4 weeks (Wills et al. 1974). Respiratory effects have been observed in dogs (Kersting and Nielson 1965) and mineralization of the pulmonary tissue has been observed in rats after l-year exposure to 1,000 mg/kg/day ethylene glycol in the feed (DePass et al. 1986a; Woodside 1982). Because of the low vapor potential of ethylene glycol under normal conditions, the inhalation hazard is relatively low. Persons exposed to ethylene glycol mists (airplane de-icing solutions, etc.), may experience some irritation of the respiratory tract.

Cardiovascular Effects. Cardiovascular system involvement in humans after ethylene glycol ingestion occurs at the same time as respiratory system involvement (Vale 1979). Tachycardia, ventricular gallop, and cardiac dilatation have been observed (Parry and Wallach 1974; Siew et al. 1975a; Vale

1979). As with the respiratory system response, cardiac symptoms occur after ingestion of large amounts of ethylene glycol in a short period of time. Dogs exhibited bradycardia and myocardial hemorrhages after an acute fatal oral dose of ethylene glycol (Kersting and Nielson 1965). Mineralization of the cardiac tissue was observed in rats after 1 year of treatment with 1,000 mg/kg/day ethylene glycol in the feed (DePass et al. 1986a; Woodside 1982). In general, however, it is unlikely that a low exposure to ethylene glycol would result in cardiac effects.

Gastrointestinal Effects. Very few data describing gastrointestinal effects of ethylene glycol exposure exist in the literature. Gastrointestinal tract bleeding was observed in a man after he had drunk a quart of ethylene glycol (Spillane et al. 1991). Mineralization of the stomach tissue was noted in male rats after exposure to 1,000 mg/kg/day ethylene glycol in the feed for 1 year (DePass et al. 1986a; Woodside 1982).

Hematological Eflects. The hematological system does not appear to be sensitive to ethylene glycol. Inhalation of 12 ppm ethylene glycol for 4 weeks did not alter hematological parameters in male volunteers (Wills et al. 1974). Most animal studies indicate no adverse effects on hematological parameters. Male rats treated orally with 1,000 mg/kg/day ethylene glycol for 1 year had reduced erythrocyte count, reduced hematocrit, and reduced hemoglobin (DePass et al. 1986a; Woodside 1982).

Musculoskeletal Effects. There were no *in vivo* studies on the effect of ethylene glycol on the musculoskeletal system. *In vitro* studies indicate that ethylene glycol affects myosin crossbridge formation necessary for muscle contraction (Mushtaq and Greene 1989). Data indicate that in the presence of ethylene glycol, rabbit skeletal myosin forms a more weakly binding complex than that which is observed in the absence of ethylene glycol. In addition, ethylene glycol appears to have a direct effect on actin molecules. Other studies indicate that in the presence of ethylene glycol, stretched rat muscle fibers exposed to photolysis and subsequent adenosine triphosphate (ATP) release exhibit a slower transition from the detached state to the force-producing state (Horiuti et al. 1992). These data suggest again that ethylene glycol affects aspects of muscle fiber crossbridge .formation (Horiuti et al. 1992). Similar results were reported after calcium-induced release of ATP from rat muscle fibers in the presence of ethylene glycol (Sakoda and Hiruiti 1992). The relevance of these musculoskeletal effects to human exposure to ethylene glycol is not clear.

Hepatic Effects. Hepatic involvement in ethylene glycol toxicity is not evident in reports of human poisoning. In general, laboratory animals do not exhibit marked adverse hepatic effects, after acute or intermediate exposure (Harris et al. 1992; Hong et al. 1988; Neeper-Bradley 1990; Price et al. 1985; Tyl 1985, 1988a; Tyl et al. 1993). Degeneration of the centrilobular hepatocytes was observed in male mice fed 6,500 mgfkglday for up to 13 weeks, whereas fatty degeneration of the liver was seen in female rats fed 200 mg/kg/day ethylene glycol for 2 years (DePass et al. 1986a; Melnick 1984; NTP 1992). Therefore, the liver may not be a sensitive indicator of ethylene glycol exposure, especially after acute exposure.

Renal Effects. Adverse renal effects have been observed in the third stage of human ethylene glycol poisoning, which occurs 24-72 hours after acute exposure. The hallmark of renal toxicity is the presence of calcium oxalate monohydrate crystals in the renal tubules, and their presence in the urine after ingestion of large amounts of ethylene glycol (Blakeley et al. 1993; Chung and Tuso 1989; Factor and Lava 1987; Godolphin et al. 1980). Focal tubular degeneration, atrophy, and tubular interstitial inflammation have also been observed (Factor and Lava 1987). Renal damage, if untreated, can lead to renal failure (Chung and Tuso 1989; Gordon and Hunter 1982; Jacobson et al. 1984; Mallya et al. 1986). With therapy, however, normal or near normal renal function can be restored. Similar renal damage has been observed in companion animals and in laboratory animals, primarily after acute exposure to high doses or intermediate or chronic exposure to lower doses (Beckett and Shields 1971; DePass et al. 1986a; Grauer et al. 1987; Melnick 1984; NTP 1992; Penumarthy and Oehme 1975; Roberts and Siebold 1969; Woodside 1982).

Body Weight Effects. Body weight does not appear to be a sensitive indicator of ethylene glycol toxicity. There were no reports of changes in body weight after ethylene glycol exposure in humans. In animals, a similar lack of effect has been observed after acute exposure. Male rats exhibit decreased body weight after exposure to 2,500 mg/kg/day ethylene glycol in the feed for 13 weeks, or 1,000 mg/kg/day in the feed for 1 year (DePass et al. 1986a; Melnick 1984; Woodside 1982). Mice exhibited decreased body weight after 1,625 mgfkg/day in the feed for 13 weeks, but no ,effect after 1,000 mg/kg/day in the feed for 2 years (DePass et al. 1986a; NTP 1992).

Metabolic Effects. One of the major adverse effects following acute oral exposure of humans to ethylene glycol is metabolic acidosis (Berger and Ayzar 1981; Blakeley et al. 1993; Cheng et al. 1987; Chung and Tuso 1989; Gordon and Hunter 1982: Heckerling 1987; Jacobsen et al. 1988). Data

indicate that glycolic acid, a metabolite of ethylene glycol, is responsible for causing metabolic acidosis and accompanying ethylene glycol toxicity (Jacobsen et al. 1984). Similar observations have been made in animals (Clay and Murphy 1977; Hewlett et al. 1989; Marshall 1982).

Immunological and Lymphoreticular Effects. Ethylene glycol does not seem to have any characteristic adverse immunological effects. There were no studies that specifically addressed immunological effects in humans or animals. Data in the literature are sparse and conflicting (DePass et al. 1986a; Spillane et al. 1991; Underwood and Bennett 1973; Wills et al. 1974; Woodside 1982). Thus, it appears unlikely that ethylene glycol exposure will cause significant immunological effects.

Neurological Effects. Few data are available describing neurological effects of dermal or inhalation ethylene glycol exposure. The data that are available indicate that acute oral intoxication is the source of the most characteristic neurological manifestations. Specifically, adverse neurological reactions are among the first symptoms to appear in human ethylene glycol poisoning. These are the only symptoms that are attributable directly to ethylene glycol, and resemble ethanol intoxication. They occur within 30 minutes to 12 hours after exposure, and include ataxia, disorientation, restlessness, slurred speech, and somnolence, progressing to convulsions and coma (Cheng et al. 1987; Factor and Lava 1987; Gordon and Hunter 1982; Robinson and McCoy 1989; Vale 1979; Woolf et al. 1992). These symptoms may be ameliorated by supportive therapy. Some evidence exists that damage to the cranial nerves may occur much later in the toxic process, especially if supportive therapy is delayed (Chung and Tuso 1989; Factor and Lava 1987; Mallya et al. 1986; Spillane et al. 1991). Similar effects have been seen in laboratory animals after large oral doses of ethylene glycol were administered (Beckett and Shields 1971; Clark et al. 1979; Penumarthy and Oehme 1975).

In vitro studies of the effect of ethylene glycol on nerve cell cultures from Wistar rats indicate that ethylene glycol caused neuronal degeneration, decreased in acetylcholinesterase-containing cells, and reactive cellular grouping (Capo et al. 1993).

Reproductive Effects. Studies have not addressed the reproductive toxicity of ethylene glycol in humans. Mice treated with 200 mg/kg/day ethylene glycol showed some degeneration of the seminiferous tubules (Hong et al. 1988). In addition, female mice orally exposed to 2,500 mg/kg/day ethylene glycol for 20 days, and mated on the eighth day of exposure with males that had been treated for 17 days prior to mating, had fewer live litters, more dead implants, and more litters totally

resorbed (Harris et al. 1992). However, male mice showed no direct effects on the reproductive system, suggesting that the effects originated with the female (Harris et al. 1992). Most other studies indicate no direct adverse effects of ethylene glycol on the reproductive organs (Depass et al. 1986a; Nagano et al. 1984).

Developmental Effects. Studies have not addressed the developmental toxicity of ethylene glycol in humans. Female mice and rats exhibit adverse effects on developmental parameters after exposure to ethylene glycol during gestation at doses of 2,100-2,500 ppm, and 400 ppm, respectively, by noseonly inhalation (Tyl 1988a), and 500 and 750 mg/kg/day, respectively, by gavage (Price et al. 1985; Tyl 1989). Rabbits receiving 2,000 mg/kg/day ethylene glycol by gavage showed no adverse developmental effects (Tyl et al. 1993). No effects were seen after dermal exposure of mice to doses up to 3,549 mg/kg (Tyl 1988b). Thus, inhalation or oral exposure during organogenesis to relatively large doses of ethylene glycol may adversely affect the developmental process. However, evidence exists in laboratory studies that these adverse effects can be eliminated by correcting the metabolic acidosis that accompanies ethylene glycol exposure (Khera 1991) (see Section 2.7). Thus, the developmental effects of ethylene glycol poisoning may be preventable with proper supportive therapy.

In vitro studies of rat embryo development indicate that ethylene glycol is embryotoxic (Grafton and Hansen 1987). Ethylene glycol added to culture medium decreased the morphological score, somite number, crown-rump length, and head length, as well as DNA and protein content of rat embryos. Absence of yolk sac circulation, absent hindlimb bud, hypoplastic telencephalon, and lack of development of the otic and optic systems were also seen in exposed embryos.

Genotoxic Effects. Studies in humans have not addressed the genotoxic effects of ethylene glycol. However, in both *in vivo* and *in vitro* laboratory studies, ethylene glycol is negative for genotoxic effects. In Fischer 344 rats that received oral doses of 40, 200, and 1,000 mg/kg/day for three generations, there were no dominant lethal mutations (DePass et al. 1986b). The *in vitro* mutagenicity studies in *Salmonella typhimurium* gave uniformly negative results (Clark let al. 1979; McCann et al. 1975; Pfeiffer and Dunkelberg 1980; Zeiger et al. 1987). No growth inhibition due to DNA damage by ethylene glycol was observed in a battery of *Escherichia coli* repair-deficient strains (McCarroll et al. 1981). Negative results were also obtained in two sets of studies when ethylene glycol was tested for gene mutation in the yeast, *Schizosaccharomyces pombe* (Abbondandolo et al. 1980), and for aneuploidy induction in the fungus, *Neurospora crassa* (Griffiths 1979, 1981). Because

of the information available in in vitro culture and animals, it is reasonable to conclude that exposure to ethylene glycol poses minimal risk of causing genotoxic effects in exposed persons. A summary of genotoxic data for ethylene glycol is presented in Tables 2-7 and 2-8.

It is reasonable to assume, therefore, that ethylene glycol poses little risk of genotoxicity.

Cancer. Studies in both humans and animals indicate that there is little carcinogenic risk after ethylene glycol exposure, although the data are scanty (Bond et al. 1985; DePass et al. 1984, 1986a; NTP 1992; Woodside 1982).

The National Toxicology Program (NTP) has not classified ethylene glycol as a carcinogen. The EPA (IRIS 1995) has not assigned ethylene glycol a weight-of-evidence classification.

Minimal Risk Levels for Propylene Glycol

Inhalation MRLs

No MRLs for acute- or chronic-duration inhalation exposure to propylene glycol were derived because data are insufficient. Only one acute-duration inhalation exposure study was found in the available literature, in which rabbits were exposed to only one dose (10% aerosol) of propylene glycol for 20 and ‘120 minutes (Konradova et al. 1978). An increased number of degenerated goblet cells in the tracheal lining was observed at both doses. Only a single study was found in the available literature for inhalation exposure to propylene glycol for chronic-duration (Robertson et al. 1947) exposure. This study did not provided enough information from which to derive an MRL.

- An MRL of 0.009 ppm has been derived for intermediate-duration (15-364 days) inhalation exposure to propylene glycol.

The MRL was based on the LOAEL of 51 ppm for nasal hemorrhaging in rats (Suber et’al. 1989). The MRL was obtained by dividing the LOAEL value by 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) and multiplying by factors to adjust the exposure from 6 hours per day (6 or 24) and 5 days per week (5 of 7) to continuous exposure. Young, healthy adult Sprague-Dawley rats were divided into 4 groups of 19 males and 19 females each. Three groups were exposed for 5 days per week, 6 hours per day for 13 weeks by

Table 2-7. Genotoxicity of Ethylene Glycol *In Vivo*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Rat (*in utero* exposure)	Dominant lethal	NA	–	DePass et al. 1986b

– = negative result; NA= not applicable

Table 2-8. Genotoxicity of Ethylene Glycol *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation	–	–	Clark et al. 1979
	Gene mutation	–	–	McCann et al. 1975
	Gene mutation	–	–	Pfeiffer and Dunkelberg 1980
	Gene mutation	–	–	Zeiger et al. 1987
Escherichia coli	DNA damage	–	–	McCarroll et al. 1981
Eukaryotic organisms:				
Schizosaccharomyces pombe	Gene mutation	–	–	Abbondandolo et al. 1980
	Aneuploidy induction	–	–	Griffiths 1979, 1981
Neurospora crassa		No data	–	Griffiths 1979, 1981

– = negative result

nose-only inhalation to mean target aerosol concentrations of 51, 321, or 707 ppm propylene glycol. The fourth, the control group, was exposed to humidified, filtered room air. Nasal hemorrhaging occurred in all exposed groups of male and female rats indicating that propylene glycol can act as a dehydrogenating agent. From week 2 to 14, the average of nasal hemorrhaging in male rats was <1, 64, 74, and 75% in controls, low-exposure, medium-exposure, and high-exposure groups, respectively. In females, the average indices were <1% in controls, 14% in the low-exposure group, and 71% in the medium and high-exposure groups. Animals recovered during non-exposure weekend periods. Similar trends were observed for ocular discharge, with females having generally less ocular discharge than males. A significant reduction in body weight of 5-7% starting on day 50 and continuing until the end of the study was observed in female rats receiving the highest dose of 707 ppm propylene glycol. Similar observation was made in the group receiving 321 ppm of propylene glycol but later in the study starting on day 64. This body weight reduction was correlated with a significant reduction in food consumption. beginning on study days 43 and 50 for the high- and medium-exposure females, respectively. Female rats exposed to 321 ppm propylene glycol had a significant decrease in white blood cell count and lymphocyte numbers. Female rats exposed to 707 ppm propylene glycol had a significant decrease in hemoglobin concentration, white blood cell count and lymphocyte numbers. Male rats in the medium (321 ppm) and high (707 ppm) groups had a significant decrease in serum sorbitol dehydrogenase and gamma-glutamyl transferase. A significant decrease in total serum protein was' observed in male rats treated with high dose (707 ppm) of propylene glycol while females treated with a medium dose (321 ppm) of propylene glycol had an increase in total serum protein. These changes were considered to be sporadic. Kidney weight was decreased at 321 ppm in both sexes. Although there were no treatment-related gross pathology changes, light microscopy revealed thickening of respiratory epithelium with increase in the number of goblet cells and their mucin content in both female and male animals receiving medium and high propylene glycol dose. Minute volume, tidal volume, and respiratory rates were not significantly altered in rats exposed to 51, 321, or 707 ppm propylene glycol for 13 weeks, suggesting that animals adapted to the exposure concentrations.

Oral MRLs

No MRLs for acute-, intermediate-, or chronic-duration oral exposure to propylene glycol were derived because data are insufficient.

Death.There were no reports in the literature of human death due to propylene glycol exposure by any route, at any level, for any length of time. Lethal oral doses for rats, mice, and guinea pigs range from 8,000 to 46,000 mg/kg (Clark et al. 1979; EPA 1987a). Monkeys died after inhalation exposure to 112 ppm propylene glycol after 13 months (Robertson et al. 1947). It is unlikely that sufficient amounts of propylene glycol would be inhaled, ingested, or absorbed through the skin to be fatal.

Systemic Effects.

Respiratory Effects. Acute respiratory arrest was observed in an 8-month-old infant being treated for second and third degree bums with an topical antibiotic formulation containing propylene glycol (Fligner et al. 1985). The contribution of the bum injury and the antibiotic therapy to the respiratory arrest, however, is not known. Anecdotal accounts of respiratory irritation after exposure to propylene glycol as a mist or vapor in theatrical productions was found in the literature (Ross01 1990). Studies of laboratory animals are inconclusive with respect to the respiratory effects of propylene glycol (Konradova et al. 1978; Suber et al. 1989).

Cardiovascular Effects. Very limited information is available in humans and animals on cardiovascular effects after exposure to propylene glycol. In the case of the 8-month-old infant mentioned above, cardiac arrest accompanied the respiratory arrest (Fligner et al. 1985). The contribution of the infant's injuries to the observed symptoms is not known. No cardiovascular effects were noted in rats after 2 years of exposure to oral doses of propylene glycol up to 49,500 ppm (Morris et al. 1942). Myocardial edema was observed in a horse prior to death from an accidental oral administration of 7,904 mg/kg propylene glycol (Dorman and Haschek 1991).

Gastrointestinal Effects. There were no reports of the effects of propylene glycol on the gastrointestinal system of humans. Propylene glycol is approved as a direct food additive. Toxicity to the gastrointestinal system has been shown to be negligible. In rats, only a very large oral dose of 23,500 mg/kg caused hemorrhagic enteritis (Clark et al. 1979). Monkeys and rats exposed by inhalation to concentrations of propylene glycol up to 112 ppm for 13-18 months had no gastrointestinal effects (Robertson et al. 1947). The effect of orally administered propylene glycol on the brush border membrane from the jejuno-ileum portion of the intestines of rats was investigated *in vivo* and *in vitro* (Morshed et al. 1991a). In rats receiving 2,942 mg/kg propylene glycol for lo-30 days, brush border enzymes including sucrase, lactase, and gamma-glutamyl transpeptidase

exhibited a tendency toward increased activity. Absorption of D-glucose and calcium was increased after 10 days of treatment, whereas absorption of D-glucose, glycine, L-aspartic acid, L-lysine, and calcium were elevated after 20 or 30 days of treatment. The structural integrity of the jejunal surface was not adversely affected. When evaluated in vitro, propylene glycol inhibited sucrase, lactase, and maltase, in a non-competitive dose-related manner, with sucrase being the most affected. Nutrient transport was not altered. These studies suggest that ingested propylene glycol may influence intestinal digestive and absorptive functions, and that the *in vivo* and *in vitro* effects are through different mechanisms.

Hematological Effects. Propylene glycol does not appear to adversely affect hematological parameters in humans (Lolin et al. 1988). In animals, however, intermediate- and chronic-duration exposure to propylene glycol may lead to hemolysis of red blood cells. For example, propylene glycol is used as a moistening agent in cat food. Studies of cats fed 1,200 mgkglday and higher doses of propylene glycol for 2-17 weeks exhibited hypocellularity of the bone marrow, increased Heinz body formation and decreased RBC survival (Christopher et al. 1989a; Weiss et al. 1990, 1992). Similar results were seen in dogs after chronic exposure to 5,000 mg/kg/day (Weil et al. 1971).

Musculoskeletal Effects. No *in vivo* data on musculoskeletal effects of propylene glycol were found in the literature. Propylene glycol was shown to cause damage with subsequent creatine kinase release from rat skeletal muscle (Brazeau and Fung 1990). Attempts to elucidate the mechanism of this damage suggested that propylene glycol-mediated damage of skeletal muscle may be caused by an intracellular mechanism rather than by a direct action on the sarcolernma, and that the mechanism may involve calcium. Frog muscle preparations exhibit increased twitch tension in the presence of propylene glycol (Hattori and Maehashi 1993). Propylene glycol appears to facilitate transmitter release from the nerve terminals and raise the acetylcholine sensitivity of the muscle endplate.

Renal Effects. No *in vivo* studies describing frank renal toxicity for propylene glycol alone were found (Christopher et al. 1989a; Gaunt et al. 1972; Robertson et al. 1947; Suber et al. 1989). Polyuria and polydipsia have been observed in cats ingesting 8,000 mg/kg/day propylene glycol for 3 or more weeks (Christopher et al. 1989a, 1990b). Propylene glycol has been shown to damage the membranes of human proximal tubule cells in culture (Morshed et al. 1994). Lactate release was increased and glucose accumulation decreased in human proximal tubule cells prior to observation of membrane

damage, indicating that damage was occurring even when the plasma membrane appeared to be unaffected.

Dermal Effects. Propylene glycol has few irritative properties in humans when applied topically, except in the case of unusual sensitivity (Aberer et al. 1993; Corrazza et al. 1993; Hannuksela et al. 1975; Kinnunen and Hannuksela 1989; Trancik and Maibach 1982; Warshaw and Herrmann 1952; Willis et al. 1989).

Body Weight Efsects. Propylene glycol has little effect on body weight. Exposure of rhesus monkeys to 112 ppm propylene glycol by inhalation for up to 13 months had no effect on body weight, whereas in the same study, rats treated to the same dose for 18 months exhibited a 50% decrease in body weight (Robertson et al. 1947). In another study, rats exposed to 321 ppm for an intermediate period of time had decreased body weight (Suber et al. 1989).

Metabolic Effects. Like ethylene glycol, propylene glycol causes acidosis, through conversion to lactic and pyruvic acids. However, the acidosis from propylene glycol is not as severe as that caused by ethylene glycol. Evidence of this comes from clinical cases of dermal or intravenous treatment with drug formulations containing propylene glycol (Fligner et al. 1985; Glasgow et al. 1983; Huggon et al. 1990; Kelner and Bailey 1985). Acidosis also occurs after ingestion of large amounts of propylene glycol (Lolin et al. 1988). Increased osmolal gap was observed in cats after ingestion of 1,600 mg/kg/day propylene glycol for 5 weeks (Christopher et al. 1990b). It seems possible that metabolic acidosis could develop in humans after exposure to large doses.

High levels of propylene glycol in the plasma can lead to an increase in the osmolal gap. Propylene glycol is oxidatively converted to lactic and pyruvic acids which, if present in sufficient amounts, contribute to a metabolic acidosis. However, acidosis from propylene glycol is not as severe as that due to ethylene glycol. An 8-month-old infant with a severe burn was topically treated with 9,000 mg/kg/day of propylene glycol used as a vehicle for silver sulfadiazine (Fligner et al. 1985). The osmolal gap reached a maximum of 130 milliosmoles/kg 14 days after the treatment started, while serum propylene glycol level peaked at 1,059 mg/dL. Due to the high dose of propylene glycol, and the possible concomitant effects of both the bum injury and the sulfadiazine therapy, the actual source of the metabolic effect in this infant could not be determined, although propylene glycol can not be ruled out as the causative agent. The bum injury may have contributed to the increased absorption of

propylene glycol and hence, the hyperosmolality. Another infant developed increased osmolality after being exposed intravenously to propylene glycol (2.4 mg/kg) used as a vehicle for Enoximone (Huggon et al. 1990). However, in another study of acute dermal propylene glycol exposure of 12 adults to 6,100 mg/kg/day for 5 days, propylene glycol had no effect on either serum osmolality or lactic acid levels (Commens 1990). Increased serum propylene glycol levels, increased lactate, and increased total acid (serum lactate and pyruvate) were also found in a retrospective study of 35 human sera samples and 8 cerebrospinal fluid samples from patients receiving intravenous medications with propylene glycol as the vehicle (Kehrer and Bailey 1985). The daily dose of propylene glycol ranged from 57 to 771 mg/kg. None of the sera samples were specifically collected for determination of propylene glycol levels; therefore, the time between propylene glycol administration and serum collection varied and was not specified in the report. However, statistically significant correlation was found between the lactate levels in serum and cerebrospinal fluid samples and the corresponding propylene glycol concentrations (Kelner and Bailey 1985). Although the results of these studies are not conclusive, it seems that increased lactate levels leading to acidosis and increased osmolality may develop in humans in the event high levels of propylene glycol are absorbed into the blood stream.

Immunological and Lymphoreticular Effects. Since propylene glycol is used in topical formulations, it has been investigated as both an irritant and contact allergen (Hannuksela et al. 1975; Kinnunen and Hannuksela 1989; Willis et al. 1988). Results indicate that except in rare cases (Corrazza et al. 1993; Hannuksela et al. 1975; Tranick and Maibach 1982) the irritative properties of propylene glycol are minimal and can not be classified as allergic reactions (Aberer et al. 1993; Hannuksela and Forstrom 1978; Willis et al. 1989). There was no effect on the spleen in rats or monkeys exposed to 112 ppm aerosolized propylene glycol for up to 18 months (Robertson et al. 1947; Suber et al. 1989).

Propylene glycol in a concentration of 0.5-1.0% has been shown to inhibit natural cytotoxicity and neutrophil chemiluminescence in human cells in vitro (Denning and Webster 1987). The authors suggest that propylene glycol has cytotoxic properties, and should be evaluated in light of this information.

Neurological Effects. Mild neurological effects have been observed in dermally sensitive individuals after an oral challenge dose of 2-15 mL of propylene glycol (Hannuksela and Forstrom 1978). In the case of ingestion of a large amount of propylene glycol, neurotoxic symptoms including

stupor and repetitive convulsions were noted (Lolin et al. 1988). Neurological effects were also noted in patients receiving 887 mg/kg propylene glycol 3 times daily, but those effects were complicated by co-ingestion of ethanol (Yu et al. 1985). Adverse effects have also been observed in rats prior to death (Clark et al. 1979), and in cats (Christopher et al. 1990b). Based on these data, however, it seems unlikely that low level exposure to propylene glycol would cause neurotoxicity.

Reproductive Effects. Studies in humans have not addressed whether propylene glycol adversely affects the reproductive system. In rats and mice, no adverse effects on the reproductive competence of these animals were observed after oral treatment as high as 10,000 mg/kg/day during gestation, or inhalation exposure to 112 ppm for 18 months (Kavlock et al. 1987; NTP 1985; Robertson et al. 1947).

Developmental Effects. Specific *in vivo* studies have not addressed the developmental toxicity of propylene glycol in humans or animals. *In vitro* studies of embryonic development suggest that propylene glycol alters the development of mouse zygotes (Damien et al. 1989, 1990). Treatment with propylene glycol caused cell membrane damage and altered pH, resulting in a decrease in embryonic development.

Genotoxic Effects. Studies in humans or animals have not addressed whether adverse genotoxic effects occur after ***in vivo*** exposure to propylene glycol. Propylene glycol was not mutagenic in S. *typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 with and without metabolic activation (Clark et al. 1979; Pfeiffer and Dunkelberg 1980). Propylene glycol was negative for sister chromatid exchange and changes in alkaline elution rate using Chinese hamster cells or human fibroblasts (Sasaki et al. 1980 as cited in Abe et al. 1982; Swenberg et al. 1976). A summary of genotoxic data for propylene glycol is presented in Table 2-9.

Cancer. There is no evidence that propylene glycol is carcinogenic in humans or animals.

The National Toxicology Program (NTP) has not classified propylene glycol as a carcinogen. The EPA (IRIS 1995) has not assigned propylene glycol a weight-of-evidence classification.

Table 2-9. Genotoxicity of Propylene Glycol *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation	–	–	Clark et al. 1979
	Gene mutation	–	–	Pfeiffer and Dunkelberg 1980
Mammalian cells:				
Human fibroblasts	Chromosome aberrations	–	–	Sasaki et al. 1980
Chinese hamster cells	Chromosome aberrations	–	–	Sasaki et al. 1980
Chinese hamster lung cells	DNA damage	–	–	Swenberg et al. 1976

– = negative result

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. Ihey have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). Biomarkers of exposure have been used by industrial hygienists in limited instances as evidence of exposure to certain chemicals. The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to ethylene glycol and propylene glycol are discussed in Section 2.4.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect have been used by clinicians to guide them in diagnoses and treatment. Biomarkers of effects caused by ethylene glycol and propylene glycol are discussed in Section 2.4.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. Biomarkers of susceptibility may be defined, for all practical purposes, as the susceptibility of the individual, relative to its own population. If biomarkers of susceptibility exist, they are discussed in Section 2.6, Populations That Are Unusually Susceptible.

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Ethylene Glycol oy Propylene Glycol

Biomarkers of exposure to a compound are of use only if they are specific to the compound in question. The biomarkers for ethylene glycol meet this criterion. Exposure to ethylene glycol can be measured by determining the levels of ethylene glycol in the blood. There are two difficulties associated with determining blood levels of ethylene glycol. The first is that ethylene glycol is absorbed and metabolized fairly rapidly in the body, which means that in most cases it is not present in the blood for more than a few hours after exposure. Second, the complex procedure needed for determination of the ethylene glycol is not always readily available in emergency situations.

Presence of ethylene glycol in the blood would indicate a very recent exposure. In humans, ethylene glycol has a relatively short half-life in the body (about 3-4 hours) (Winek et al. 1978), and thus, only exposures that occurred 10-20 hours earlier would be detected in the blood. Ethylene glycol concentrations in urine are higher than ethylene glycol concentrations in serum, and thus, remain detectable for a longer period. Rapid methods for determining ethylene glycol in serum and urine are available for use in the clinical setting (Aarstad et al, 1993; Blandford and Desjardins 1994). The information on ethylene glycol levels in bodily fluids has been scarce until recently because gas chromatography, which is most often used for ethylene glycol determination (see Chapter 6 for details), has not always been available to an emergency department physician. In general, ethylene glycol blood levels show no direct correlation with degree of toxicity (Jacobsen and McMartin 1986). Values in case reports have varied from 14.5 mg/dL (Underwood and Bennett 1973) to 650 mg/dL (Peterson et al. 1981). The great variation results from differences in the amounts of ethylene glycol consumed and in the time delays between ingestion and blood sampling (Jacobsen and McMartin 1986; Peterson et al. 1981; Rothman et al. 1986; Underwood and Bennett 1973; Walton 1978).

Because ethylene glycol is rapidly absorbed and biotransformed in the body, some of its metabolic products may be used to identify exposure to ethylene glycol. Metabolic acidosis due to increased amounts of glycolic acid and lactic acid occurs in cases of intoxication with ethylene glycol (Jacobsen et al. 1984). However, lactic acid is not a specific marker for ethylene glycol exposure, and thus, has no use as a biomarker in this instance. In cases of exposure to ethylene glycol, there is a small increase in the amount of oxalic acid in blood, contributing to metabolic acidosis. As oxalic acid interacts with calcium from the body, it forms calcium oxalate crystals which can be detected in the urine (Jacobsen et al. 1988). Accumulation of glycolic acid primarily accounts for the acidosis of ethylene glycol intoxication; its presence can indicate significant exposure, even when the ethylene glycol blood levels are very low (Hewlett et al. 1986; Jacobsen et al. 1984). Glycolic acid can be used as a relatively sensitive indicator of ethylene glycol exposure, due to its relatively high production from ethylene glycol and its rapid clearance from the body. Rapid and accurate methods of analysis now exist for glycolic acid in serum (Fraser and MacNeil 1993). Calcium oxalate is a less sensitive marker, due to its slow formation and its relatively slow clearance from the body. Both serum glycolic acid and urinary calcium oxalate have been used to identify exposure to ethylene glycol.

Propylene glycol can also be detected in the blood a short time after exposure to a large amount. There are no other specific biomarkers for propylene glycol exposure. Since propylene glycol is considered a safe additive for food, cosmetics, and pharmaceuticals, other specific tests of propylene glycol exposure have not been developed.

2.5.2 Biomarkers Used to Characterize Effects Caused by Ethylene Glycol or Propylene Glycol

Adverse neurological reactions that can culminate in convulsions and coma are among the first symptoms in humans after ethylene glycol intoxication (Zeiss et al. 1989). Some of the most common manifestations of ethylene glycol neurotoxicity include ataxia, slurred speech, semiconsciousness, unresponsiveness, and somnolence (Anonymous 1987; Cheng et al. 1987; Chung and Tuso 1989; Factor and Lava 1987; Parry and Wallach 1974; Rothman et al. 1986; Spiilane et al. 1991; Underwood and Bennett 1973). Several more recent studies described adverse effects of ethylene glycol on cranial nerves; the symptoms appear later and may involve facial paralysis, bilateral optic nerve dysfunction, and peripheral neurosensory hearing loss. These symptoms are not specific to ethylene glycol, but in conjunction with known or suspected exposure, may serve to guide diagnosis and treatment.

2. HEALTH EFFECTS

The presence of calcium oxalate monohydrate crystals is the hallmark of ethylene glycol intoxication. The crystals can be deposited in renal tubules and/or excreted in urine after exposure to relatively large amounts of ethylene glycol (Anonymous 1987; Chung and Tuso 1989; Factor and Lava 1987; Godolphin et al. 1980; Heckerling 1987; Parry and Wallach 1974; Rothman et al. 1986; Siew et al. 1975a; Underwood and Bennett 1973). In some cases, there is only a brief period of calcium oxalate dihydrate crystalluria (Jacobsen et al. 1988). Renal toxicity can also be indicated by increased serum levels of BUN or creatinine; however, this occurs relatively late in intoxication (i.e., stage 3, 48-72 hours after ethylene glycol ingestion) and is not specific for ethylene glycol intoxication (Grauer et al. 1987).

Respiratory system involvement occurs 12-24 hours after ingestion of ethylene glycol. The symptoms include hyperventilation (Godolphin et al. 1980), shallow rapid breathing (Zeiss et al. 1989), and generalized pulmonary edema (Vale 1979).

Cardiovascular system involvement occurs during the second phase of ethylene glycol poisoning, at the same time as the respiratory system involvement. The symptoms are tachycardia, ventricular gallop, and ventricular dilation (Parry and Wallach 1974; Siew et al. 1975a; Vale 1979). As in the case of respiratory effects, cardiovascular involvement occurs after exposure to relatively high oral levels of ethylene glycol. Both of these types of effects are not specific to ethylene glycol intoxication.

Propylene glycol is not associated with any specific biomarkers of effect. Dermal irritation may occur after repeated exposure, and suspect drug or cosmetic preparations should be examined closely for propylene glycol content.

For more information on biomarkers for renal and hepatic effects of chemicals see *ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage* (1990) and for information on biomarkers for neurological effects see OTA (1990).

2.6 INTERACTIONS WITH OTHER CHEMICALS

Information regarding the influence of other chemicals on the toxicity of ethylene glycol comes from case studies describing treatment after accidental or intentional ingestion of ethylene glycol. The toxic effects of ethylene glycol result from its metabolic conversion by alcohol dehydrogenase into glycolic

acid which is further metabolized to oxalate. The formation of oxalate crystals is associated with renal toxicity encountered after exposure to ethylene glycol. Administration of ethanol, 4-methyl pyrazole (also used as antidotes in cases of methanol poisoning), or 1,3-butanediol reduces or eliminates ethylene glycol toxicity. This is accomplished by the following mechanisms: 1) ethanol, which is also metabolized by alcohol dehydrogenase, competes with ethylene glycol for the enzyme, thus preventing the formation of potentially toxic ethylene glycol metabolites; 2) 4-methyl pyrazole inhibits the activity of alcohol dehydrogenase (Baud et al. 1987, 1988); and 3) 1,3-butanediol is also a competitive inhibitor of ethylene glycol biotransformation and reduces the formation of glycolic acid (Hewlett et al. 1983). Therefore, ethanol, 4-methyl pyrazole, and 1,3-butanediol reduce the toxicity of ethylene glycol by interacting with or inhibiting the activity of alcohol dehydrogenase, thus reducing the amount of glycolic acid and oxalate formed.

Magnesium and vitamin B6 were found to affect the toxicity of ethylene glycol in animals. In rats, vitamin B6 accelerates the oxidation of glyoxylate to carbon dioxide rather than to oxalate (Gershoff and Audrus 1962). Vitamin B6 deficiency can cause inhibition of ethylene glycol's oxidation to carbon dioxide and, thus cause an increase in ethylene glycol toxicky. Magnesium may prevent renal deposition of calcium oxalate by altering solvent characteristics of oxalate in urine (Browning 1965; Gershoff and Andrns 1962; Khan et al. 1993).

Ethylene glycol has been shown to be a substrate for rat liver microsomal cytochrome P-450 *in vitro* (Kukielka and Cederbaum 1991). If such activity were to occur *in vim,* ethylene glycol may interact with the metabolism of many drugs that would be substrates for the same enzyme.

In the first step of biotransformation, propylene glycol is catalyzed by alcohol dehydrogenase, as in the case of ethylene glycol. 4-Methyl pyrazole is an inhibitor of propylene glycol metabolism (Morshed et al. 1988). As in the case of ethylene glycol, 4-methyl pyrazole may reduce potential toxic effects of propylene glycol and act as an antidote by interfering with the biodegradation of propylene glycol.

Review of the literature regarding the interaction and influence of other chemicals on the toxicity of propylene glycol revealed that propylene glycol is often used as a vehicle for administration of certain medications such as Valium, Dilantin, Nembutal (Kemer and Bailey 1985), dihydrotachysterol (DHT) (Arulanantham and Gene1 1978), Ketoconazo1e.crean.r (Eun and Kim 1989), and Enoximone (Huggon et al. 1990). Among the observed effects were seizures and cerebral irritability (DHT), increased

serum lactate (Valium, Dilantin, and Nembutal), increased serum osmolality (Enoximone), and skin allergy (Ketoconazole cream). All these adverse effects are attributed to propylene glycol and associated with the prolonged administration of these medications using propylene glycol as the vehicle. However, the precise interaction between propylene glycol and these medications was not investigated.

In rats, hexobarbital-induced sleeping time was prolonged in the presence of propylene glycol (Dean and Stock 1974), probably because of competition for drug-metabolizing enzymes. Studies in rabbits have shown that propylene glycol inhibited the elimination of 8-chlorotheophylline and dimenhydrinate from the blood, due to a diminished metabolism of the two drugs (Walters et al. 1993).

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to ethylene glycol and propylene glycol compared to most persons exposed to the same level of ethylene glycol and propylene glycol in the environment. Reasons include genetic makeup, developmental stage, health and nutritional status, and chemical exposure history. These parameters may result in decreased function of the detoxification and excretory processes (mainly hepatic and renal) or compromised function of target organs. For these reasons, the elderly with declining organ function, people with unusual chemical exposure history, heavy users of alcohol, and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Because of its sweet taste, easy access, and frequent improper storage and disposal, ethylene glycol may present a particular hazard to small children. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, Populations With Potentially High Exposure.

The review of literature regarding toxic effects of ethylene glycol revealed that individuals deficient in vitamin B6 may be more sensitive to toxic effects of ethylene glycol because vitamin-B6 may reduce the accumulation of toxic metabolites (Browning 1965; Gershoff and Andrus 1962). Similarly, magnesium deficiency appears to encourage calcium oxalate deposition in the renal tubules, especially in the presence of high calcium levels (Ebisuno et al. 1987). Thus, individuals who are deficient in magnesium and/or ingest high levels of calcium may be more sensitive to the toxic effects of ethylene glycol.

No information was found on populations with unusual sensitivity to propylene glycol. However, populations that may show increased sensitivity include very young children, who have immature hepatic detoxification systems, and individuals with impaired liver or kidney function. Studies of burn patients indicate the absorption of propylene glycol from antibiotic preparations can be correlated with total bum surface area and the severity of the bum (Kulick et al. 1985). Thus, bum patients may be at a higher risk for possible adverse effects of propylene glycol. In addition, propylene glycol has been found in the blood of alcoholics with cirrhosis of the liver, in the absence of measurable blood alcohol (Casazza et al. 1987). Thus, alcoholics with liver disease may comprise a population that is unusually susceptible to the effects of propylene glycol.

2.8 METHODS FOR REDUCING TOXIC EFFECTS

2.8.1 Reducing Peak Absorption Following Exposure

No studies were found describing methods to reduce peak absorption of ethylene glycol after inhalation exposure. After oral exposure, gastric lavage or charcoal absorption can be helpful in reducing absorption. Dermal absorption can be minimized through washing the skin with soap to remove any existing ethylene glycol.

No studies on reducing peak absorption of propylene glycol after inhalation exposure were found. The pharmacokinetic properties of propylene glycol are not completely understood, but absorption from the gastrointestinal tract after oral exposure is fairly rapid. The maximum plasma concentration of propylene glycol in humans is reached within 1 hour after oral exposure, while the elimination half-life is about 4 hours. The total body clearance is about 0.1 L/kg/hour and seems to be serumconcentration dependent (Yu et al. 1985). Dose-dependent elimination is seen in rats, with saturation of the pathways at doses above 5,880 mg/kg (Morshed et al. 1988). However, no studies on reducing peak absorption following oral exposure were found.

Studies on the dermal absorption of propylene glycol in rats indicate that absorption into the dermis is enhanced by the addition of fatty acids (Takeuchi et al. 1993, 1995). Thus, cleaning of the skin with a defatting solvent, followed by washing with water, may reduce absorption of propylene glycol after dermal exposure.

2.8.2 Reducing Body Burden

Methods for reducing the body burden of ethylene glycol after oral exposure include hemodialysis (Parry and Wallach 1974). No data describing methods of reducing the body burden of ethylene glycol after inhalation or dermal exposure were found, although it would seem that the hemodialysis would also work in these instances.

No methods for reducing the body burden of propylene glycol after inhalation, oral, or dermal exposure were found.

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

Metabolic acidosis is a common symptom of ethylene glycol toxicity. The primary therapies are aimed at this toxic effect. Clinical case histories from accidental and intentional ingestion of ethylene glycol show that metabolic acidosis can be controlled and eliminated. Administration of bicarbonate to correct the blood pH, and ethanol to compete for the enzymes that convert ethylene glycol to glycolic acid, can prevent any sequelae of ethylene glycol poisoning if administered early enough. Fluid therapy and volume expansion, and diuresis are also important treatments for ethylene glycol poisoning. Peritoneal and hemodialysis are useful therapies for reducing the toxic effects of ethylene glycol. In laboratory studies, Khera (1991) has shown that in rats, correction with bicarbonate of metabolic acidosis caused by ethylene glycol administration (up to 5,000 mg/kg orally on Gd 11) reduced or prevented subsequent developmental anomalies. Thus, proven methods of reducing the toxic effects of ethylene glycol exist and can be used in the event of a toxic exposure.

Male Porton rats receiving 999-1,110 mg/kg ethylene glycol in the drinking water for 21 days exhibited significantly increased renal calcium oxalate deposition when given diets supplemented with 30 or 60% sucrose (Rofe et al. 1986). The authors hypothesized that the increased levels of sugar or sugar alcohol as a result in increased carbohydrates in the diet, increase the supply of calcium in the renal medulla, leading to increased calcium oxalate deposition. The increased supply of calcium may be the result of decreased reabsorption in the tubules, or increased release due to increased energy supply from the carbohydrate metabolism. This study suggests that administering a diet low in carbohydrates may be helpful in reducing calcium oxalate deposition in the kidneys after ethylene glycol exposure.

Magnesium and vitamin B6 were found to affect the toxicity of ethylene glycol in animals. In rats, vitamin B6 accelerates the oxidation of glyoxylate to carbon dioxide rather than to oxalate (Gershoff and Andrus 1962). Vitamin B6 deficiency can cause inhibition of ethylene glycol's oxidation to carbon dioxide and, thus cause an increase in ethylene glycol toxicity. Magnesium may prevent renal deposition of calcium oxalate by altering solvent characteristics of oxalate in urine (Browning 1965; Gershoff and Andrus 1962; Khan et al. 1993). Magnesium deficiency, especially in the presence of increased calcium intake, has been shown to accelerate renal tubular calcium oxalate deposition (Ebisuno et al. 1987). Thus, administration of magnesium may aid in preventing calcium oxalate deposition in the kidneys after ethylene glycol exposure.

Renal calcium oxalate deposition in rats after ethylene glycol exposure has been shown to increase in the presence of high levels of dietary calcium (Ebisuno et al. 1987). Administration of phytin or citrate appears to inhibit calcium oxalate deposition in the renal tubules. Thus, phytin or citrate may be a useful dietary agent for the prevention of adverse renal effects after ethylene glycol ingestion, especially in the presence of high calcium levels.

4-Methyl pyrazole, an alcohol dehydrogenase inhibitor, effectively blocks the metabolism of ethylene glycol to toxic intermediates and has been shown to be effective in preventing renal effect of ethylene glycol after ingestion (Baud et al. 1987, 1988; Dial et al. 1989, 1994). Thus, administration of 4-methyl pyrazole may be an effective treatment for preventing renal failure after ethylene glycol exposure.

Toxicity studies of propylene glycol in laboratory animals can be found in the literature, but findings of adverse effects are rare. Clinical studies in the literature consist of infrequent sensitivity reactions, primarily to drug preparations, where pre-existing conditions requiring the drug come into play. There are two main reasons for that: 1) propylene glycol biodegradation proceeds via lactate to pyruvate in human metabolism, and 2) a significant amount of propylene glycol is excreted unchanged or as glucuronide conjugate via the renal pathway (Hammksela and Forstrijm 1978). Propylene glycol exhibits few of the toxic properties of ethylene glycol. Since, however, it does cause metabolic acidosis, albeit to a lesser extent that ethylene glycol, correction of the acid-base imbalance would also be helpful in preventing subsequent effects.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of ethylene glycol and propylene glycol is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of ethylene glycol and propylene glycol.

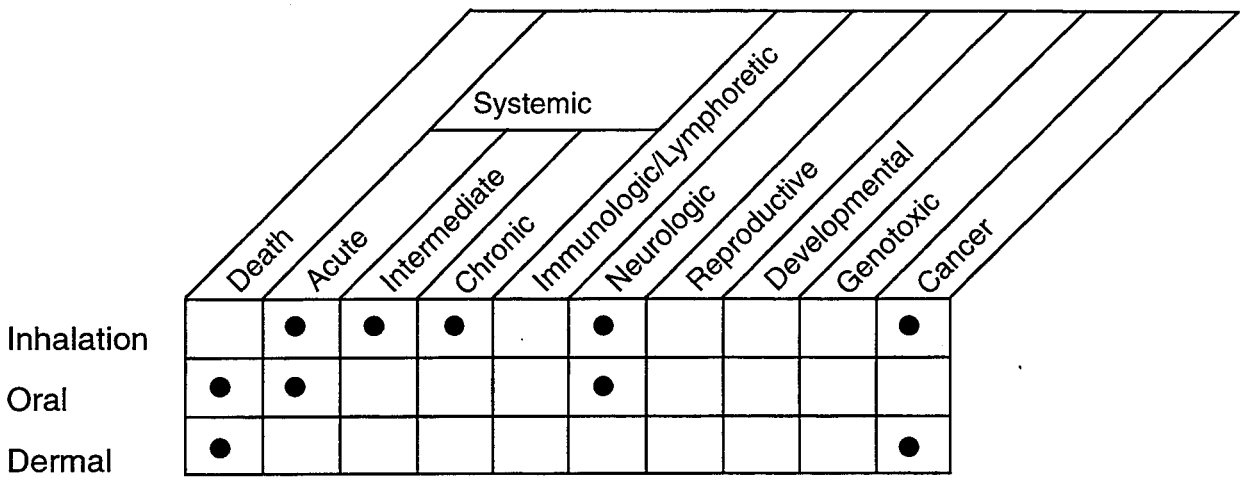
The following categories of possible data needs have been identified by scientists from ATSDR. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be fulfilled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be prepared.

2.9.1 Existing Information on Health Effects of Ethylene Glycol and Propylene Glycol

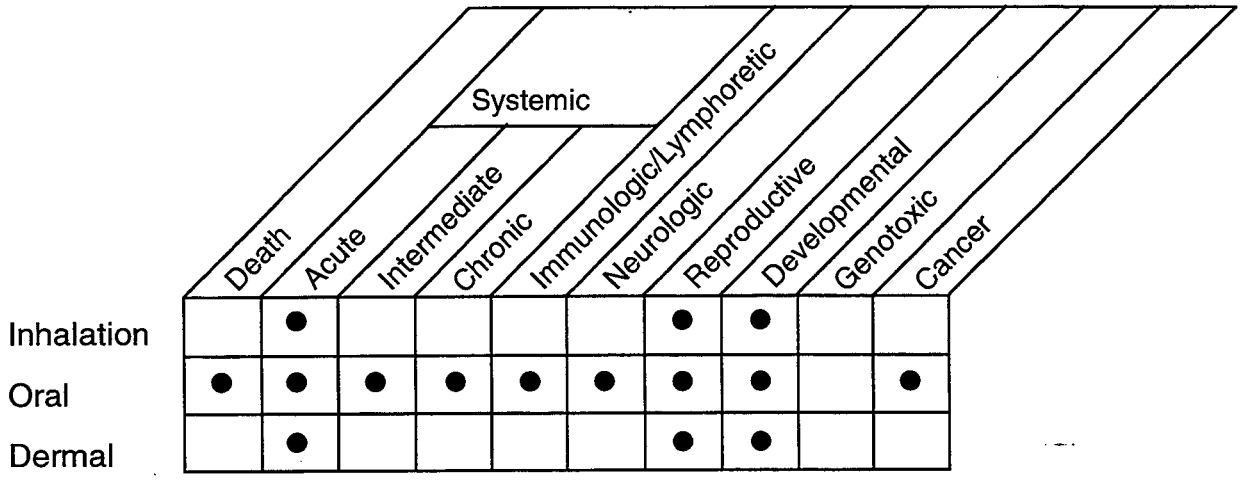
Existing information on health effects of ethylene glycol is shown in Figure 2-7, and existing information on the health effects of propylene glycol is shown in Figure 2-8. The purpose of these figures is to illustrate the existing information concerning the health effects of ethylene glycol and propylene glycol, respectively. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature..

The literature reviewed for health effects of ethylene glycol in humans came from one set of experimental data of acute-to-intermediate exposure of a group of 20 volunteers, one report of industrial exposure, and one epidemiological study of renal cancer mortality. Biological data, including hematology and blood chemistry, urinalysis, reports of respiratory irritation, and cancer

Figure 2-7. Existing Information on Health Effects of Ethylene Glycol



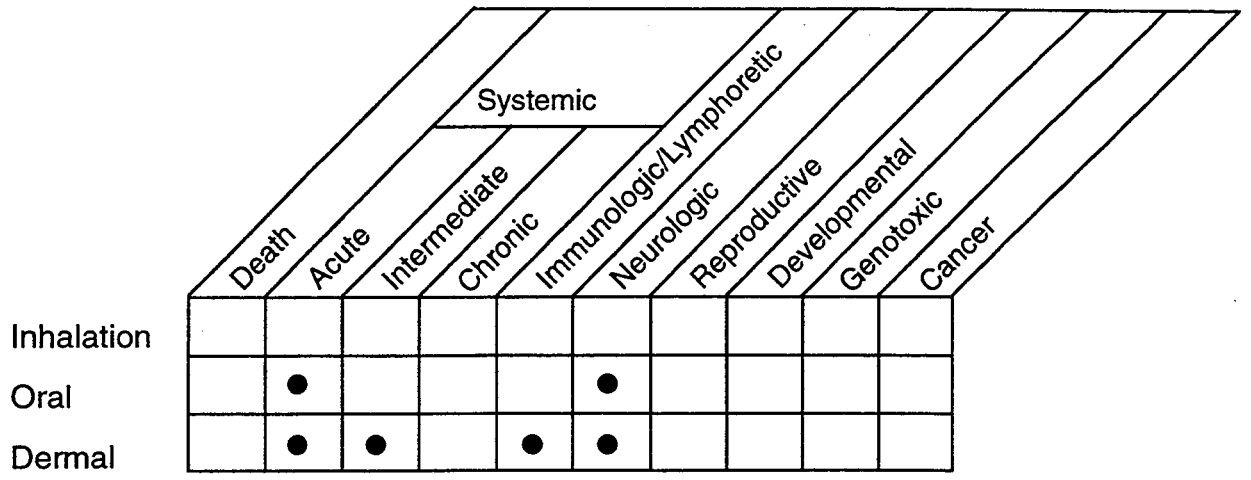
Human



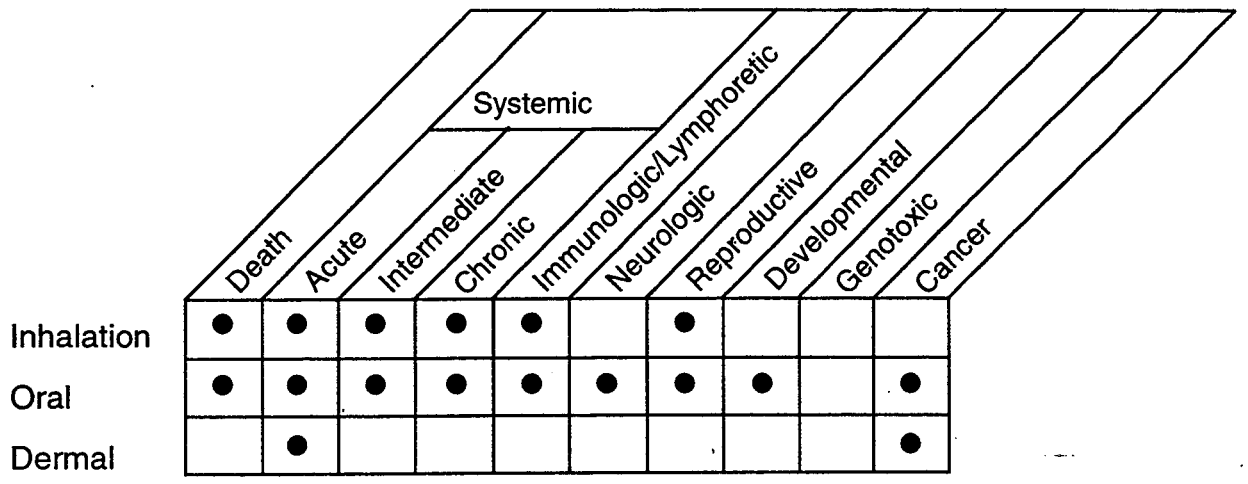
Animal

● Existing Studies

Figure 2-8. Existing Information on Health Effects of Propylene Glycol



Human



Animal

● Existing Studies

mortality were recorded. With the exception of the study of volunteers, no exposure levels could be determined from these reports. Therefore, the information on human inhalation exposure to ethylene glycol is limited. Data in animals for inhalation exposure is limited to two studies of developmental toxicity in rodents.

The database for the health effects of ethylene glycol following oral administration in humans and animals is more substantial. With respect to human exposure, case reports of accidental or intentional ingestion comprise the entire database. In these instances, exposure levels are not exact. Reports of oral exposure in animals are more complete and provide data for every health effect category, with the exception of *in vivo* measures of genotoxicity.

No reliable data describing health effects of ethylene glycol after dermal exposure in humans were found. A single report of occupational exposure was found, but the route of exposure and exposure level were not specified. Data describing health effects of ethylene glycol after dermal exposure in animals was contained in a single report of acute toxicity and one report of developmental toxicity.

People living near hazardous waste sites or near sites where ethylene glycol is manufactured or used in high volume (e.g., as a de-icing agent) may be exposed to ethylene glycol by ingestion of contaminated water, or by dermal contact with contaminated materials. In addition, inhalation or dermal exposure may occur in workers involved in high volume applications of ethylene glycol. Accidental or intentional ingestion of ethylene glycol remains a source of exposure, as does dermal exposure through handling of antifreeze solutions during automobile maintenance. Dermal exposure is the least likely route to cause toxicity, and can easily be prevented by using protective clothing. The health effects of oral exposure are fairly well documented, through accidental and intentional poisoning, and from animal studies. Therefore, inhalation exposure through high volume use remains the area likely to cause human health effects for which there is little data.

There is very little data on health effects of propylene glycol in humans. No data for humans were found for inhalation exposure of humans. Data exist for inhalation exposure of animals for acute-, intermediate-, and chronic-duration exposure.

Some acute oral data exist for humans, but the information is scanty and includes systemic, and neurological effects after acute exposure. Propylene glycol is considered GRAS by the FDA, and thus

oral exposure through foods is considered safe. With respect to this, animal data for oral exposure are more extensive, and all categories of health effects except in vivo genotoxicity are included.

Propylene glycol is used extensively in topical drug formulations and cosmetics. The majority of reports of human dermal studies describe sensitivity reaction (or, lack of reaction) to these preparations. Human dermal data includes acute-duration effects, and immunological and neurological effects. Animal data describing dermal exposure are limited to acute-duration effects and an evaluation of immunological and neurological effects.

People living near hazardous waste sites or near sites where propylene glycol is manufactured may be exposed to propylene glycol by ingestion of contaminated water. Since propylene glycol is an approved food additive, ingestion of small amounts would not be considered a health risk. Inhalation exposure is not a likely route for toxic health effects. Dermal exposure to propylene glycol has been associated with sensitivity reactions, although the data are confusing. Increased use of propylene glycol in foods and cosmetics, and as a substitute for ethylene glycol suggests that general exposure to propylene glycol will be more frequent and at higher levels than previously experienced by the general population. Therefore, additional research in these areas may be warranted.

2.9.2 Identification of Data Needs

Acute-Duration Exposure. Little information is available regarding the effects of acute-duration respiratory exposure to ethylene glycol in humans. Only one study exists in the literature, describing health effects of 20 volunteers after acute-duration inhalation exposure (Wills et al. 1974). Respiratory irritation was observed during the acute-duration exposure, but no other effects were reported. Two reports were found describing acute-duration inhalation exposure of rats and mice (Tyl 1985, 1988a). More reports of acute-duration oral exposure were found for humans (Berger and Ayyar 1991; Blakely et al. 1993; Cheng et al. 1987; Chung and Tuso 1989; Factor and Lava 1987; Godolphin et al. 1980; Gordon and Hunter 1982; Heckerling 1987; Hewlett et al. 1986; Jacobsen et al. 1984, .1988; Karlson-Stiber and Pen-son 1992; Mallya et al. 1986; Oliver0 1993; Parry and Wallach 1974; Peterson et al. 1981; Rothman et al. 1986; Siew et al. 1975a; Spillane et al. 1991; Underwood and Bennett 1973; Walton 1978; Woolf et al. 1992; Zeiss et al. 1989) and animals (Adams et al. 1991; Beckett and Shields 1971; Clark et al. 1979; Clay and Murphy 1977; Dial et al. 1989; Ebisuno et al. 1987; Grauer et al. 1987; Harris et al 1992; Hong et al. 1988; Kersting and Nielsen 1965; Man- et al. 1992; Neeper-

Bradley 1990; NTP 1988; Penumarthy and Oehme 1975; Price et al. 1985; Richardson 1973; Roberts and Seibold 1969; Schuler et al. 1984; Tyl 1989; Tyl et al. 1993). No studies of acute-duration dermal exposure to ethylene glycol in humans were found, although two studies in animals were located (Clark et al. 1979; Tyl 1988b).

Death can occur in humans after ingestion of ethylene glycol (Godolphin et al. 1980; Gordon and Hunter 1982; Hewlett et al. 1986; Jacobsin et al. 1984; Siew et al. 1975a; Zeiss et al. 1989), and also in animals (Adams et al. 1991; Beckett and Shields 1971; Clark et al. 1979; Kersting and Nielson 1965; Penumarthy and Oehme 1975; Richardson 1973; Schuler et al. 1984; Tyl et al. 1993). The main targets of ethylene glycol toxicity following acute exposure are the kidney and the developing fetus (Adams et al. 1991; Beckett and Shields 1971; Berger and Ayyar 1981; Blakely et al. 1993; Chung and Tuso 1989; Ebisuno et al. 1987; Factor and Lava 1987; Godolphin et al. 1980; Gordon and Hunter 1982; Heckerling 1987; NTP 1988; Price et al. 1985; Roberts and Seibold 1969; Schuler et al. 1984; Tyl 1989; Tyl et al. 1988a).

An acute-duration MRL was derived for inhalation exposure to ethylene glycol based on increased kidney weight in mice (Tyl et al. 1988a). An acute-duration MRL was derived for oral exposure, based on developmental toxicity in mice (Tyl 1989). Additional acute-duration dermal studies may be helpful in evaluating this route of exposure.

No information was available for acute-duration inhalation exposure to propylene glycol in humans. Only one study in animals was found to provide some information for acute-duration inhalation exposure (Konradova et al. 1978). Rabbits were exposed to only one dose (10% aerosol) of propylene glycol for 20 or 120 minutes, and an increased number of degenerated goblet cells in the tracheal lining was observed. No other data were available from this study and the importance of these findings is unclear. Information regarding acute-duration oral exposure to propylene glycol in humans (Frosch et al. 1990; Hannuksella and Forstrom 1978; Lolin et al. 1988; Nelson et al. 1987) and animals is more abundant (Clark et al. 1979; Dorman and Haschek 1991; Kavlock et al:1987; Morshed et al. 1991a; Ruddick 1972; Studer et al. 1993; Weiss et al. 1992). Acute-duration dermal exposure to propylene glycol in humans (Commens 1990; Corazza et al. 1993; Eun and Kim 1989; Fligner et al. 1985; Kinnunen and Hannuksela 1989; Kulick et al. 1985; Willis et al. 1988) and animals has been reported (Clark et al. 1979), although data are scarce.

Death has been shown to occur after acute-duration oral exposure to propylene glycol (Clark et al. 1979; Dorman and Haschek 1991; Gordon and Hunter 1982; Ruddick 1972). With the exception of hematological effects in cats after oral exposure (Weiss et al. 1992), there does not appear to be a target system for propylene glycol effects. Sensitization reactions have been reported in humans after acute-duration dermal exposure (Corazza et al. 1993; Hannuksella and Forstrom 1978).

No acute-duration inhalation MRL could be derived for propylene glycol because no adequate studies were found. In the single acute-duration inhalation study found in the literature (Konradova et al. 1978), only one dose was used, and sufficient information was not provided on which to base and MRL. No acute-duration oral MRL could be derived for propylene glycol because no adequate studies were found. With regard to the human studies (Frosch et al. 1990; Hannuksella and Forstrom 1978; Lolin et al. 1988; Nelson et al. 1987), only one dose was tested, data were sparse, or the exact dose was not known. Acute-duration oral studies in animals focused on death (Clark et al. 1979; Ruddick 1972), involved a single dose (Dorman and Haschek 1991; Kavlock et al 1987; Morshed et al. 1991a; Studer et al. 1993), or discussed species-specific effects (Weiss et al. 1992). Thus, none of these studies were adequate for deriving an MRL.

Intermediate-Duration Exposure. Only one study describing intermediate-duration inhalation exposure of humans to ethylene glycol was found (Wills et al. 1974), and no studies were found for animals. Oral intermediate-duration exposure data for ethylene glycol was not found for humans, but is more abundant for animals (DePass et al. 1986b; Harris et al. 1992; Khan et al. 1993; Lamb et al. 1985; Melnick 1984; Nagano et al. 1984; NTP 1992; Roberts and Seibold 1969; Rofe et al. 1986). No data were found for intermediate-duration dermal exposure to ethylene glycol in either humans or animals.

Death has been reported after intermediate-duration oral exposure to ethylene glycol in rats (Melnick et al. 1984). As in the acute-duration studies, renal (DePass et al. 1986b; Khan et al. 1993; Melnick 1984; NTP 1992; Roberts and Seibold 1969; Rofe et al. 1986) and reproductive and deiielopmental toxicity (Harris et al. 1992; Lamb et al. 1985) were observed in animals after intermediate-duration exposure.

No intermediate-duration inhalation or oral MRLs could be derived for ethylene glycol because no appropriate studies were found. With regard to inhalation exposure, the intermediate-duration portion

of the study (Wills et al. 1974) did not provide an adverse effect level for less serious effects that could be attributed to ethylene glycol. For oral exposure, all appropriate and adequate studies found (DePass et al. 1986b; Harris et al. 1992; Khan et al. 1993; Lamb et al. 1985; Melnick 1984; NTP 1992; Roberts and Seibold 1969; Rofe et al. 1986) had NOAELs and LOAELs that were higher than the NOAEL and LOAEL in the study chosen for the acute-duration oral MRL (Tyl et al. 1988a).

No studies of intermediate-duration inhalation exposure of humans to propylene glycol were found. One intermediate-duration inhalation study of propylene glycol in rats was found in the literature (Suber et al. 1989). No studies of intermediate-duration oral exposure of humans to propylene glycol were found. Studies of intermediate-duration oral exposure of animals were more abundant (Bauer et al. 1991; Christopher et al. 1989a; Morshed et al. 1991a; NTP 1985; Weiss et al. 1990). No studies of intermediate-duration dermal exposure to propylene glycol were found in animals. One intermediateduration dermal exposure study in humans described primarily dermal irritative effects of propylene glycol (Trancik and Maibach 1982).

No reports of death in animals after intermediate-duration exposure to propylene glycol were found. Systemic effects after inhalation exposure of rats included nasal hemorrhaging, hematological effects, and decreased kidney and body weight (Suber et al. 1989). Cats exhibit characteristic hematotoxicity (Heinz body formation) after intermediate-duration oral exposure (Bauer et al. 1991; Christopher et al. 1989a; Weiss et al. 1990), although no other targets for toxicity were apparent.

An intermediate-duration inhalation MRL was derived for propylene glycol based on nasal hemorrhaging in rats (Suber et al. 1989). No intermediate-duration oral MRL could be derived due to a lack of suitable studies. Of the intermediate-duration oral exposure studies found, none were in humans; animal studies included species-specific effects in cats (Bauer et al. 1991; Christopher et al. 1989a; Weiss et al. 1990), studies with a single dose (Morshed et al. 1991a), or studies with no adverse effects observed (NTP 1985).

Chronic-Duration Exposure and Cancer. Few studies were found describing chronic-duration inhalation exposure to ethylene glycol in humans, and no studies were found describing chronicduration inhalation exposure to ethylene glycol in animals. One report of an industrial exposure by inhalation over a period of 2 years described hematological and neurological effects, but an exposure level could not be determined (Triosi 1950). In the other study describing chronic occupational

exposure, the renal cancer mortality rate of a cohort of former employees of a chemical plant was determined (Bond et al. 1985); exposure level was not determined in this study either. Thus, human data for chronic inhalation exposure is scanty.

No studies of chronic-duration oral exposure to ethylene glycol in humans were found. Several chronic-duration oral exposure animal studies were found (Blood 1962, 1965; DePass et al. 1984, 1986a; Morris et al. 1942; NTP 1992; Woodside 1982).

Only one study was found that could be classified as chronic-duration dermal exposure to ethylene glycol (Bond et al. 1985). In this epidemiological study of renal cancer mortality, dermal exposure in the occupational setting is assumed. Exposure levels were not determined. No chronic-duration dermal studies of ethylene glycol in animals were found.

Death was observed in rats after chronic-duration oral exposure to ethylene glycol in the feed (Blood 1965; DePass et al. 1986a; Morris et al. 1942; Woodside 1982). Death rates were 70-100% after exposure to doses of 500 mgkglday or greater for more than 12 months. Males were more sensitive than females. Death was not observed in humans after chronic-duration inhalation or dermal exposure (Bond et al. 1985; Triosi 1950). After chronic-duration inhalation exposure of women working in a factory, increased lymphocyte count was found (Triosi 1950). In the other study describing chronic occupational exposure, the renal cancer mortality rate of a cohort of former employees of a chemical plant was determined and found not to be correlated with inhalation exposure to ethylene glycol (Bond et al. 1985).

Data describing systemic effects from chronic-duration oral exposure in animals is more abundant. No adverse effects on the histopathology of tissues, including kidneys, were observed in rhesus monkeys exposure to 200 mg/kg day ethylene glycol in the feed for 3 years (Blood et al. 1962). Male rats exposed to 500 mg/kg/day ethylene glycol in the feed for 2 years exhibited oxalate crystals and proteinuria prior to death, whereas female rats exposed to ethylene glycol in the same study exhibited these renal effects at 2,000 mg/kg/day (Blood 1965). The sensitivity of the male rat to the renal effects of ethylene glycol were also observed by DePass et al. (1986a), and Woodside (1982). Male Fischer rats exhibited oxalate nephrosis and chronic nephritis after exposure to 1,000 mg/kg/day ethylene glycol in the feed for 12 months, whereas females only exhibited elevated urinary oxalate at the same dose. Adverse renal effects, including kidney stones, tubular atrophy, and tubular casts were

also noted by Morris et al. (1942) after chronic oral exposure to ethylene glycol. Other effects noted in rats included decreased hematocrit, reduced REK, reduced hemoglobin, and increased neutrophils in males (DePass et al. 1986a; Woodside 1982), fatty metamorphosis of the liver in females (Depass et al. 1986a; Woodside 1982), and hepatic atrophy and bile duct proliferation (Morris et al. 1942). Mice appear to be less sensitive to the toxic effects of orally administered chronic-duration ethylene glycol. No adverse effect on liver, kidney, or other organ systems was observed in CD-1 mice exposed to 1,000 mg/kg/day ethylene glycol in the feed for 2 years (DePass et al. 1984). Only after exposure to doses of 1,625 mg/kg/day or greater for 2 years were adverse effects, including pulmonary arterial medial hyperplasia, hyaline degeneration of the centrilobular hepatocytes, and oxalate nephrosis observed in mice (NTP 1992). In this study, also, males were more sensitive than females (NTP 1992). No evidence of increased tumorigenesis was observed in the oral chronic-duration rodent studies (DePass et al. 1984, 1986a; NTP 1992; Woodside 1982).

No chronic-duration inhalation MRL could be derived due to a lack of appropriate studies. A chronicduration oral MRL was derived based on renal toxicity in male rats after chronic exposure to ethylene glycol in the feed (DePass et al. 1986a; Woodside 1992). .

No chronic-duration studies of human exposure to propylene glycol alone by inhalation, oral, or dermal administration were found in the literature. One study of chronic-duration inhalation exposure of animals (Robertson et al. 1947), and one study of dermal exposure of animals (Stenback and Shubik 1974) were found. Data for chronic-duration oral exposure of animals to propylene glycol is more abundant (Gaunt et al. 1972; Morris et al. 1942; Weil et al. 1971). Tumorigenesis was evaluated after inhalation and dermal exposure (Robertson et al. 1947; Stenback and Shubik 1974).

After inhalation exposure to propylene glycol for 13 months, 13 of 29 rhesus monkeys died (Robertson et al. 1947). Death was not observed in rats or dogs after exposure to oral doses of propylene glycol of 2,500 or 5,000 mg/kg/day, respectively, for 2 years (Gaunt et al. 1972; Weil et al. 1971). No reports of death after dermal exposure were found. Systemic effects noted after inhalation. exposure of animals to propylene glycol were few, and included increased hemoglobin in monkeys and increased body weight in rats (Robertson et al. 1947). Similarly, only hematological effects, including decreased erythrocytes, hemoglobin, and hematocrit were observed in dogs at 5,000 mg/kg/day (Weil et al. 1971).

No evidence of tumorigenesis was noted after oral exposure of rats to doses of propylene glycol up to 2,500 mg/kg/day for 2 years (Gaunt et al. 1972), or dermal exposure of mice to 20 mg applied twice weekly for 120 weeks (Stenback and Shubik 1974).

No MRLs for chronic-duration inhalation exposure to propylene glycol could be derived due to a lack of appropriate studies in the literature. No studies were found for humans, and in the one animal study found (Robertson et al. 1947), the effects cited (increased hemoglobin and body weight) were not appropriate effects on which to base an MRL. No MRLs for chronic-duration oral exposure to propylene glycol could be derived due to a lack of appropriate studies in the literature. In the one study found (Gaunt et al. 1972), no adverse effects were noted.

Immunological and Lymphoreticular Effects. Ethylene glycol does not seem to have any characteristic adverse immunological effects. There were no studies that specifically addressed immunological effects in humans or animals. Data in the literature are sparse and conflicting (DePass et al. 1986a; Spillane et al. 1991; Underwood and Bennett 1973; Wills et al. 1974; Woodside 1982). Further evaluation of the immunological and lymphoreticular effects of ethylene glycol would be useful in assessing the effects of ethylene glycol exposure by inhalation, oral, and dermal routes.

Since propylene glycol is used in topical formulations, it has been investigated as both an irritant and contact allergen (Hannuksela et al. 1975; Kinnunen and Hannuksela 1989; Tranick and Maibach 1982; Willis et al. 1988). Results indicate that except in rare cases (Corrazza et al. 1993; Hannuksela et al. 1975; Trancik and Maibach 1982) the irritative properties of propylene glycol are minimal (Aberer et al. 1993; Hannuksela and Forstrom 1978; Willis et al. 1989). There was no effect on the spleen in rats or monkeys exposed to 112 ppm aerosolized propylene glycol for up to 18 months (Robertson et al. 1947; Suber et al. 1989).

Propylene glycol in a concentration of 0.5-1.0% has been shown to inhibit natural cytotoxicity and neutrophil chemiluminescence in human cells *in vitro* (Denning and Webster 1987). The authors suggest that propylene glycol has cytotoxic properties and should be evaluated in light of this information.

The data describing the immunotoxicity of propylene glycol is not clear. Further *in vivo* animal studies would be helpful in defining the immunotoxic effects of propylene glycol.

Neurological Effects. Few data are available describing neurological effects of dermal or inhalation ethylene glycol exposure. The data that are available indicate that acute oral intoxication is the source of the most characteristic neurological manifestations. Specifically, adverse neurological reactions are among the first symptoms to appear in human ethylene glycol poisoning. These are the only symptoms that are attributable directly to ethylene glycol, and resemble ethanol intoxication. They occur within 30 minutes to 12 hours after exposure, and include ataxia, disorientation, restlessness, slurred speech, and somnolence, progressing to convulsions and coma (Cheng et al. 1987; Factor and Lava 1987; Gordon and Hunter 1982; Robinson and McCoy 1989; Vale 1979; Woolf et al. 1992). These symptoms may be ameliorated by supportive therapy. Some evidence exists that damage to the cranial nerves may occur much later in the toxic process, especially if supportive therapy is delayed (Chung and Tuso 1989; Factor and Lava 1987; Mallya et al. 1986; Spillane et al. 1991). Similar effects have been seen in laboratory animals after large oral doses of ethylene glycol were administered (Beckett and Shields 1971; Clark et al. 1979; Penumarthy and Oehme 1975). In vitro studies of the effect of ethylene glycol on nerve cell cultures from Wistar rats indicate that ethylene glycol caused neuronal degeneration, decreased in acetylcholinesterase-containing cells, and reactive cellular grouping (Capo et al. 1993). The neurological effects of ethylene glycol after oral exposure appear to be fairly well defined. Further studies of this route of exposure are not warranted. However, little or no data are available describing neurological effects after inhalation or dermal exposure to ethylene glycol. Additional data for these routes of exposure would be helpful in comparing the potential for neurological effects after inhalation or dermal exposure with the welldefined effects observed after oral exposure.

Mild neurological effects have been observed in dermally sensitive individuals after an oral challenge dose of 2-15 mL of propylene glycol (Hannuksela and Forstrom 1978). In the case of ingestion of a large amount of propylene glycol, neurotoxic symptoms including stupor and repetitive convulsions were noted (Lolin et al. 1988). Neurological effects were also noted in patients receiving 887 mg/kg propylene glycol 3 times daily, but those effects were complicated by co-ingestion of ethanol (Yu et al. 1985). Adverse effects have also been observed in rats prior to death (Clark et al. 1979) and in cats (Christopher et al. 1990b). Based on these data, however, it seems unlikely that low level exposure to propylene glycol would cause neurotoxicity. Further studies of the neurological effects of propylene glycol would be helpful in defining the toxicity of the compound.

Reproductive Toxicity. Studies have not addressed the reproductive toxicity of ethylene glycol in humans. Mice showed some degeneration of the seminiferous tubules after oral exposure (Hong et al. 1988). In addition, female mice orally exposed to ethylene glycol for 20 days, and mated on the eighth day of exposure with males that had been treated for 17 days prior to mating, had fewer live litters, more dead implants, and more litters totally resorbed (Harris et al. 1992). However, male mice showed no direct effects on the reproductive system, suggesting that the effects originated with the female (Harris et al. 1992). In a multi-generation continuous breeding study done in CD-l mice (Lamb et al. 1985), intermediate exposure to 1% ethylene glycol in drinking water slightly decreased the fertility of the exposed parental and F_1 generations. Most other studies indicate no direct adverse effects of ethylene glycol on the reproductive organs (Depass et al. 1986a; Nagano et al. 1984). Ethylene glycol does not appear to cause direct effects on the reproductive tissues, and further studies are not warranted.

Studies in humans have not addressed whether propylene glycol adversely affects the reproductive system. In rats and mice, no adverse effects on the reproductive competence of these animals were observed after oral treatment at doses as high as 10,000 mgkglday during gestation of 1 generation or for multiple litters and 2 generations of mice (Kavlock et al. 1987; NTP 198.5) or inhalation exposure to 112 ppm for 18 months (Robertson et al. 1947). Further evaluation of the reproductive toxicity of propylene glycol is not necessary.

Developmental Toxicity. Studies have not addressed the developmental toxicity of ethylene glycol in humans. Female mice and rats exhibit adverse effects on developmental parameters after exposure to ethylene glycol during gestation at doses of 2,100-2,500 ppm or 400 ppm, respectively, by nose-only inhalation (Tyl 1988a), and 500 or 750 mg/kg/day by gavage (Price et al. 1985; Tyl 1989). Rabbits receiving 2,000 mg/kg/day ethylene glycol by gavage showed no adverse developmental effects (Tyl et al. 1993). No effects were seen after dermal exposure of mice to doses up to 3,549 mg/kg (Tyl 1988b). Thus, inhalation or oral exposure during organogenesis to relatively large doses of ethylene glycol may adversely affect the developmental process. However, ev”ldence exists in laboratory studies that these adverse effects can be eliminated by correcting the metabolic acidosis that accompanies ethylene glycol exposure (Khera 1991) (see Section 2.7). Thus, the developmental effects of ethylene glycol poisoning may be preventable with proper supportive therapy.

In vitro studies of rat embryo development indicate that ethylene glycol is embryotoxic (Grafton and Hansen 1987). Ethylene glycol added to culture medium decreased the morphological score, somite number, crown-rump length, and head length, as well as DNA and protein content of rat embryos. Absence of yolk sac circulation, absent hindlimb bud, hypoplastic telencephalon, and lack of development of the otic and optic systems were also seen in exposed embryos. The developmental toxicity of ethylene glycol is fairly well defined. Further evaluation of the developmental toxicity of ethylene glycol toxicity is not warranted.

Propylene glycol does not appear to be a developmental toxicant in animals. Pregnant female Swiss mice given 10,000 mg/kg/day propylene glycol by mouth on Gd 8-12 showed no adverse developmental effects (Kavlock et al. 1987). No adverse effects of propylene glycol on the development of Swiss (CD-l) mice were noted after doses of approximately 10,000 mg/kg/day (NTP 1985). *In vitro* studies of embryonic development suggest that propylene glycol alters the development of mouse zygotes (Damien et al. 1989, 1990). Treatment with propylene glycol caused cell membrane damage and altered pH, resulting in a decrease in embryonic development. The relevance of these results to *in vivo* exposure is not clear. Further studies of developmental toxicity of propylene glycol do not appear to be necessary.

Genotoxicity. Although neither ethylene glycol or propylene glycol has been extensively evaluated in genetic toxicity test systems, the existing studies provide convincing evidence that neither compound is genotoxic. Ethylene glycol was negative for dominant lethal mutations in rats (DePass et al. 1986b), S. *typhimurium* assays gave uniformly negative results (Clark et al. 1979; McCann et al. 1975; Pfeiffer and Dunkelberg 1980; Zeiger et al. 1987), and no growth inhibition due to DNA damage by ethylene glycol was observed in a battery of *E. coli* repair-deficient strains (McCarroll et al. 1981). Negative results were also obtained in two sets of studies when ethylene glycol was tested for gene mutation in the yeast *S. pombe* (Abbondandolo et al. 1980), and for aneuploidy induction in the fungus N. C~USSU (Griffiths 1979, 1981). Because of the information available in *in vitro* culture and animals, it is reasonable to conclude that exposure to ethylene glycol poses minimar risk of causing genotoxic effects in exposed persons, and that no further studies are necessary.

Studies in humans or animals have not addressed whether adverse genotoxic effects occur after *in vivo* exposure to propylene glycol. However, propylene glycol was not mutagenic in *S. typhimurium* strains with and without metabolic activation (Clark et al. 1979; Pfeiffer and Dunkelberg 1980). In addition,

propylene glycol was negative for sister chromatid exchange and changes in alkaline elution rate using Chinese hamster cells or human fibroblasts (Sasaki et al. 1980 as cited in Abe et al. 1982; Swenberg et al. 1976). Based on these results, it seems likely that propylene glycol does not represent a genotoxic risk to exposed persons. An in *vivo* study would complete the database of the genotoxic effects of propylene glycol.

Epidemiological and Human Dosimetry Studies. No reliable epidemiological studies of ethylene glycol exposure are available. Individuals who work with ethylene glycol in high volume applications, such as de-icing aircraft and routine automobile maintenance, are the populations most likely to be at risk for toxic effects. Epidemiological and human dosimetry studies.after inhalation and dermal exposure would be helpful in further evaluating ethylene glycol toxicity in these subpopulations.

No reliable epidemiological studies of propylene glycol exposure are available. Increased use of propylene glycol in food and in drugs and cosmetics suggests that oral and dermal exposure are the most important routes of exposure for the general population. In addition, the substitution of propylene glycol in applications where ethylene glycol was previously used will create new subpopulations for exposure. Bpidemiological and human dosimetry studies of these subpopulations would be helpful in evaluating propylene glycol toxicity in these increased applications of use.

Biomarkers of Exposure and Effect.

Exposure. Exposure to ethylene glycol can be measured by determining the levels of ethylene glycol in the blood. Presence of ethylene glycol in the blood would indicate a very recent exposure. Since ethylene glycol blood levels show no direct correlation to the degree of toxicity, blood levels are only of value in establishing exposure. Ethylene glycol concentrations in urine are higher than ethylene glycol concentrations in serum; thus, it remain detectable for a longer period. Rapid methods for determining ethylene glycol in serum and urine are available for use in the clinical setting (Aarstad et al. 1993; Blandford and Desjardins 1994).

Because ethylene glycol is rapidly absorbed and biotransformed in the body, some of its metabolic products may be used to identify exposure to ethylene glycol. Metabolic acidosis due to increased amounts of glycolic acid and lactic acid occurs in cases of intoxication with ethylene glycol (Jacobsen

et al. 1984). However, lactic acid is not a specific marker for ethylene glycol exposure; thus, it has no use as a biomarker in this instance. In cases of exposure to ethylene glycol, there is a small increase in the amount of oxalic acid in blood, contributing to metabolic acidosis. As oxalic acid interacts with calcium from the body, it forms calcium oxalate crystals which can be detected in the urine (Jacobsen et al. 1988). Glycolic acid can be used as a relatively sensitive indicator of ethylene glycol exposure due to its relatively high production from ethylene glycol and its rapid clearance from the body. Rapid and accurate methods of analysis now exist for glycolic acid in serum (Fraser and MacNeil 1993). Calcium oxalate is a less sensitive marker due to its slow formation and its relatively slow clearance from the body. Both serum glycolic acid and urinary calcium oxalate have been used to identify exposure to ethylene glycol. Further studies of biomarkers of exposure to ethylene glycol are not a data need.

Propylene glycol can also be detected in the blood a short time after exposure to a large amount. There are no other specific biomarkers for propylene glycol exposure. Since propylene glycol is considered a safe additive for food, cosmetics, and pharmaceuticals, other specific tests of propylene glycol exposure have not been developed. Further evaluation of possible biomarkers of exposure to propylene glycol would be helpful, especially in light of increased use of propylene glycol in food, cosmetics, and drugs.

Effect. Adverse neurological reactions that can culrnmate in convulsions and coma are among the first symptoms in humans after ethylene glycol intoxication (Zeiss et al. 1989). Some of the most common manifestations of ethylene glycol neurotoxicity include ataxia, slurred speech, semiconsciousness, unresponsiveness, and somnolence (Anonymous 1987; Cheng et al. 1987; Chung and Tuso 1989; Factor and Lava 1987; Parry and Wallach 1974; Rothman et al. 1986; Spillane et al. 1991; Underwood and Bennett 1973). Several more recent studies described adverse effects of ethylene glycol on cranial nerves; the symptoms appear later and may involve facial paralysis, bilateral optic nerve dysfunction, and peripheral neurosensory hearing loss. These symptoms are not specific to ethylene glycol, but in conjunction with known or suspected exposure, may serve to guide diagnosis and treatment.

The presence of calcium oxalate monohydrate crystals is the hallmark of ethylene glycol intoxication. The crystals can be deposited in renal tubules and/or excreted in urine after exposure to relatively large amounts of ethylene glycol (Anonymous 1987; Chung and Tuso 1989; Factor and Lava 1987; Godolphin et al. 1980; Heckerling 1987; Parry and Wallach 1974; Rothman et al. 1986; Siew et al.

1975a; Underwood and Bennett 1973). In some cases, there is only a brief period of calcium oxalate dihydrate crystalluria (Jacobsen et al. 1988). Renal toxicity can also be indicated by increased serum levels of BUN or creatinine; however, this occurs relatively late in intoxication (i.e., stage 3, 48-72 hours post ethylene ingestion) and is not specific for ethylene glycol intoxication (Grauer et al. 1987).

Respiratory system involvement occurs 12-24 hours after ingestion of ethylene glycol. The symptoms include hyperventilation (Godolphin et al. 1980), shallow rapid breathing (Zeiss et al. 1989), and generalized pulmonary edema (Vale 1979).

Cardiovascular system involvement occurs during the second phase of ethylene glycol poisoning, at the same time as the respiratory system involvement. The symptoms are tachycardia, ventricular gallop, and ventricular dilation (Parry and Wallach 1974; Siew et al. 1975a; Vale 1979). As in the case of respiratory effects, cardiovascular involvement occurs after exposure to relatively high oral levels of ethylene glycol. Both of these types of effects are not specific to ethylene glycol intoxication. Further evaluation of biomarkers of ethylene glycol effects is not a data need.

Propylene glycol is not associated with any specific biomarkers of effect. Dermal irritation may occur after repeated exposure, and suspect drug or cosmetic preparations should be examined closely for propylene glycol content. In light of the increased use of propylene glycol in foods, cosmetics, and drugs, identification of biomarkers of propylene glycol effect would be useful in evaluating biological effects of propylene glycol exposure.

Absorption, Distribution, Metabolism, and Excretion. No kinetic data for absorption, distribution, metabolism, or excretion in humans or animals of ethylene glycol after inhalation exposure were found in the literature. Since human exposure to ethylene glycol is usually oral by accidental means, or intentional ingestion (Godolphin et al. 1980; Gordon and Hunter 1982; Hewlett et al. 1986; Jacobsen et al. 1984, 1988; Karlson-Stilber and Persson 1992; Litovitz et al. 1990, 1991; Peterson et al. 1981; Siew et al. 1975a; Walton 1978; Zeiss et al. 1989) or dermal contact, without records of the amount ingested, few data describing the complete kinetics of ethylene glycol after human oral exposure were found in the literature, and no data describing the kinetics of *in vivo* human dermal exposure were found in the literature.

2. HEALTH EFFECTS

There are several human studies (Cheng et al. 1987; Hewlett et al. 1986; Jacobsen et al. 1984, 1988; Peterson et al. 1981; Rothman et al. 1986), and a number of animal studies describing absorption, distribution, metabolism, and excretion of ethylene glycol after in viva oral or dermal exposure (Dial et al. 1989, 1994; Frantz et al. 1989, 1991; Hewlett at al. 1989; Martis et al. 1982; Rofe et al. 1986; Winek et al. 1978). Information is available to assess the relative rates and extent of these parameters by the oral route in humans and animals and, to a lesser extent, by the dermal route in humans *in vitro* and in animals *in vivo* and *in , vitro.* All of the toxicokinetic data involve acute exposures to ethylene glycol. No data deal with intermediate- or chronic-duration exposures. Intermediate- and chronicduration data are needed in order to adequately assess the rates and extent of the toxicokinetic parameters for these durations. No data were located regarding the absorption, distribution, and excretion of ethylene glycol after inhalation exposure. Acute-, intermediate-, and chronic-duration exposure data are needed to adequately assess the relative rates and extent of the toxicokinetic parameters by this route. No data were located for the toxicokinetic parameters of ethylene glycol exposure in humans after dermal contact. In light of the uses of ethylene glycol, data regarding *in vivo* human exposure would be helpful in evaluating relative risk of exposure by this route.

No kinetic data for absorption, distribution, metabolism, or excretion in humans or animals of propylene glycol after inhalation exposure were found in the literature. Few data were found in the literature describing the kinetics of propylene glycol in humans after oral exposure (Yu et al. 1985), but more data were found for animals (Christopher et al. 1990b; Huff 1961; Miller and Bazzano 1965; Morshed et al. 1988, 1989, 1991a). Since propylene glycol is used in topical drug preparations, limited data are available for kinetic parameters in humans after dermal exposure (Fligner et al. 1985; Kulick et al. 1985; Rigg and Barry 1990), and in animals (Rigg and Barry 1990; Takeuchi et al. 1993, 1995). Most of these data concern acute exposures and are limited because propylene glycol is considered a safe and innocuous compound. No data were located regarding kinetic parameters of propylene glycol after inhalation exposure. Studies are needed in order to adequately assess the rates and extent of the toxicokinetic parameters for this route. In light of increased use of propylene glycol as a food additive, and in cosmetics and topically applied drugs, additional studies of the absorption, distribution, metabolism, and excretion of propylene glycol after oral and dermal exposure for acute-, intermediate-, and chronic-duration exposure would be helpful in assessing the kinetic properties of the compound by these routes.

2. HEALTH EFFECTS

Comparative Toxicokinetics. The absorption, distribution, metabolism, and excretion of ethylene glycol have been studied in animals (Dial et al. 1989, 1994; Frantz et al. 1989, 1991; Hewlett at al. 1989; Martis et al. 1982; Rofe et al. 1986; Winek et al. 1978), and to a lesser extent in humans (Cheng et al. 1987; Hewlett et al. 1986; Jacobsen et al. 1984, 1988; Peterson et al. 1981; Rothman et al. 1986). The target organs identified in humans include the kidney and neurological system. The target organs identified in animals included the kidney and developing fetus. Ethylene glycol causes metabolic acidosis in both humans and animals. Based on data in both humans and animals, ethylene glycol toxicity is the result of metabolic acidosis and calcium oxalate production. Prevention of these toxic effects can be accomplished by interfering with the metabolism of ethylene glycol. Most of the toxicokinetic studies, have been conducted using rats, since mice appear to be less sensitive and less like humans with regard to toxic sequelae after ethylene glycol exposure. Based on the available data, humans would be expected to handle ethylene glycol in a manner similar to rats, although data indicate that predictions based on rodent data tend to overestimate human response.

The kinetics of propylene glycol have been studied in animals (Morshed et al. 1988; Rigg and Barry 1990; Takeuchi et al. 1993, 1995) and to a lesser extent in humans (Fligner et al. 1985; Kulick et al. 1985; Rigg and Barry 1990; Yu et al. 1985). However, information on the toxicokinetic properties of propylene glycol are limited, based on its nontoxic status. No specific target organs have been identified for propylene glycol, although neurological effects have been noted after oral exposure (Clark et al. 1979; Hannuksela and Forstom 1978; Lolin et al. 1988; Yu et al. 1985). Propylene glycol also causes metabolic acidosis, although to a lesser extent than ethylene glycol (Lolin et al. 1988; Morshed et al. 1989, 1991b). Little data exist to assist in interspecies comparison of kinetic parameters. In light of increased use of propylene glycol in foods, cosmetics, and drugs, and as a substitute for ethylene glycol, additional inhalation, oral, and dermal kinetic studies would be helpful in predicting human kinetic response to propylene glycol exposure.

Methods for Reducing Toxic Effects. Clinical methods for reducing ethylene glycol absorption after oral exposure include gastric lavage, charcoal slurry, or emesis. However, no studies on reducing peak absorption following inhalation or dermal exposure were found. Cleaning the skin after dermal exposure would be essential in reducing absorption.

Metabolic acidosis is a common symptom of ethylene glycol toxicity. The primary therapies are aimed at this toxic effect. Clinical case histories from accidental and intentional ingestion of ethylene

glycol show that metabolic acidosis can be controlled and eliminated. Administration of bicarbonate to correct the blood pH, and ethanol to compete for the enzymes that convert ethylene glycol to glycolic acid, can prevent any sequelae of ethylene glycol poisoning if administered early enough. Fluid therapy and volume expansion, and diuresis are also important treatments for ethylene glycol poisoning. Peritoneal and hemodialysis are useful therapies for reducing the toxic effects of ethylene glycol. In laboratory studies, Khera (1991) has shown that in rats, correction with bicarbonate of metabolic acidosis caused by ethylene glycol administration reduced or prevented subsequent developmental anomalies. Thus, proven methods of reducing the toxic effects of ethylene glycol exist and can be used in the event of a toxic exposure. Rofe et al. (1986) found that coadministration of a diet supplemented with sucrose increased renal calcium oxalate deposition in rats. This study suggests that administering a diet low in carbohydrates may be helpful in reducing calcium oxalate deposition in the kidneys after ethylene glycol exposure.

Magnesium and vitamin B6 have been found to reduce the toxicity of ethylene glycol in animals (Browning 1965; Gershoff and Andrus 1962; Khan et al. 1993), whereas a deficiency of these essential nutrients accelerates toxicity (Ebisuno et al. 1987; Gershoff and Andrus 1962). Thus, administration of magnesium may aid in preventing calcium oxalate deposition in the kidneys after ethylene glycol exposure. Renal calcium oxalate deposition in rats after ethylene glycol exposure has been shown to increase in the presence of high levels of dietary calcium (Ebisuno et al. 1987). Administration of phytin or citrate appears to inhibit calcium oxalate deposition in the renal tubules. Thus, phytin or citrate may be a useful dietary agent for the prevention of adverse renal effects after ethylene glycol ingestion, especially in the presence of high calcium levels. Therefore, some data exist on dietary factors that may influence ethylene glycol toxicity. Further studies on these factors and others that may be useful in a clinical setting would be helpful in increasing the number of treatments that are beneficial in reducing the toxic effects of ethylene glycol.

4-Methyl pyrazole, an alcohol dehydrogenase inhibitor, effectively blocks the metabolism of ethylene glycol to toxic intermediates, and has been shown to be effective in preventing renal effect of ethylene glycol after ingestion (Baud et al. 1987, 1988; Dial et al. 1989, 1994). Additional studies to identify other metabolic inhibitors would be useful in adding to the treatments available for reducing or preventing the toxic effects of ethylene glycol.

No studies related to reducing absorption of propylene glycol after inhalation or oral exposure were found. Studies on the dermal absorption of propylene glycol in rats indicate that absorption into the dermis is enhanced by the addition of fatty acids (Takeuchi et al. 1993, 1995). Thus, cleaning of the skin with a defatting solvent, followed by washing with water, may reduce absorption of propylene glycol after dermal exposure.

Toxicity studies of propylene glycol in laboratory animals can be found in the literature, but findings of adverse effects are rare. Clinical studies in the literature consist of infrequent sensitivity reactions, primarily to drug preparations, where pre-existing conditions requiring the drug come into play. There are two main reasons for that: 1) propylene glycol biodegradation proceeds via lactate to pyruvate in human metabolism, and 2) a significant amount of propylene glycol is excreted unchanged or as glucuronide conjugate via the renal pathway (Hannuksela and Forstrom 1978). Propylene glycol exhibits few of the toxic properties of ethylene glycol. Since it does cause metabolic acidosis, although to a lesser extent that ethylene glycol, correction of the acid-base imbalance would also be helpful in preventing subsequent effects, and the same therapies that are useful in preventing ethylene glycol acidosis would also be useful for propylene glycol. Since propylene glycol is significantly less toxic than ethylene glycol, extensive study of methods to reduce the possible toxic effects of exposure does not seem warranted.

2.9.3 Ongoing Studies

The following ongoing studies regarding the health effects of ethylene glycol and propylene glycol were reported .in the Federal Research in Progress File (FEDRIP 1995) database and in recent literature:

Alcohol and Pyrazole Reaction and Metabolism (in vitro). The principle investigator is Arthur Cederbaum, II from Mount Sinai School of Medicine, New York, New York. The objective is to study the biochemical and pharmacological properties of pyrazole and 4-methyl pyrazole and their enzymatic loci for metabolism, in relation to their use in ethylene glycol poisoning.

Cryopreservation of Bovine Oocytes Matured in vitro. The principal investigator is J. Parks from the Cornell University School of Animal Science, Ithaca, New York. The objective is to develop practical

procedures for the cryopreservation of developmentally competent bovine oocytes. Ethylene glycol will be used as one of the cryoprotective compounds.

Evaluation of ethylene glycol poisoning continues. In a recent publication, Hylander et al. (1995) suggest that patients with severe ethylene glycol intoxication resulting in severe acidosis, hyperkalemia, and coma upon admission to a hospital have a dismal prognosis, and that other factors are unimportant to the outcome. The authors suggest that large amounts of bicarbonate, alcohol, and hemodialysis be instituted immediately and maintained, and that the renal damage more closely resembles acute tubular necrosis rather than oxalate nephropathy.

Other studies in recent literature include a study of *in vitro* penetration of ethylene glycol through human and mouse skin (Sun et al. 1995). The study was undertaken to further define absorption of ethylene glycol through human and animal skin, since dermal exposure is the most common route for humans. Preliminary results indicate that human skin is 3040 times less permeable to ethylene glycol than mouse skin. In addition, absorption of a 50% aqueous solution is approximately twice as slow in both mice and humans, compared to absorption of undiluted ethylene glycol. The authors conclude that the potential toxicity resulting from cutaneous exposure to ethylene glycol would be significantly less for humans than predicted by dermal studies in mice. In addition, aqueous solutions pose less of a hazard for dermal exposure than does undiluted ethylene glycol. Camey et al. (1995) published preliminary results of a study designed to determine if glycolic acid acts as the proximate toxicant for ethylene glycol developmental toxicity in rat whole embryo culture. Rat embryos were cultured in media containing ethylene glycol or glycolic acid at concentrations equivalent to maternal plasma concentrations observed at a NOAEL, LOAEL, or teratogenic dose in viva. Ethylene glycol was without effect in culture. Glycolic acid inhibited embryo growth, and caused death. Dysmorphogenesis was observed at the higher dose. Lowering the pH in the media exacerbated the effects, The results of this study suggests that glycolic acid acts as an intrinsic developmental toxicant and through the induction of metabolic acidosis.

Regulation of Lipid Metabolism in High Producing Dairy Cattle. The principal investigator is R. Grummer from the University of Wisconsin School of Dairy Science in Madison, Wisconsin. The objective is to determine the regulation of lipid metabolism in adipose tissue, liver and mammary glands of high producing dairy cattle. Propylene glycol will be used for reducing plasma nonesterified fatty acids during feed restriction.

2. HEALTH EFFECTS

Modifying Milk Fat Composition for Improved Manufacturing Qualities and Consumer Acceptability. The principal investigator is D. Palmquist from Ohio State University School of Animal Sciences in Wooster, Ohio. The objective is to identify and characterize important regulatory steps in fatty acid synthesis and desaturation and their positional distribution on glycerol in milk fat, and to quantify modification of milk fat composition by manipulating the diet of the cow. Propylene glycol will be used as an oral drench to modify energy balance.

Microbial Safety Criteria for Foods Contacting Reuse Water in Food. The principal investigator is A. Miller from the Eastern Regional Research Center in Wyndmoor, Pennsylvania. The objective is to identify microbiological risks to food by reuse water during slaughter and further processing, to study bacterial attachment mechanisms and develop approaches to dislodge or prevent adhesion of pathogens to food surfaces, and to investigate the potential for expanded applications of reuse water to the food plant environment. Propylene glycol will be evaluated in the control of microbial growth.

The Effect of Vitamin E on the Propylene Glycol-Induced Formation of Heinz Bodies. The principal investigator is Diane Hatchell from the Department of Veterans Affairs Medical Center, Durham, North Carolina. The objective is to test the efficacy of vitamin E as a means of inhibiting the propylene glycol-induced formation of Heinz bodies in cat blood.

3. CHEMICAL AND PHYSICAL INFORMATION

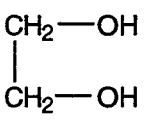
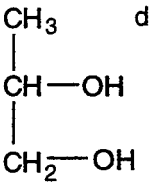
3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of ethylene glycol and propylene glycol is located in Table 3- 1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of ethylene glycol and propylene glycol is located in Table 3-2.

TABLE 3-1. Chemical Identity of Ethylene Glycol and Propylene Glycol

Characteristic	Ethylene glycol[a]	Propylene glycol[b]
Chemical name	Ethylene glycol	Propylene glycol
Synonym(s)	1,2-Dihydroxyethane; 1,2-ethandiol; 1,2-ethane-diol; 2-hydroxyethanol; ethane-1,2-diol; ethylene; alcohol; ethylene dihydrate; glycol; monoethylene glycol; MEG.	1,2-Dihydroxypropane; 1,2-propanediol; 1,2-propylene glycol; 2,3-propanediol; hydroxy-propanol; alpha-propylene glycol; methyl glycol; methylethyl glycol; monopropylene glycol; trimethyl glycol.
Registered trade name(s)	Dowtherm®	PG-12; Sirlene
Chemical formula	$C_2H_6O_2$	$C_3H_8O_2$
Chemical structure	 [c]	 [d]
Identification numbers:		
CAS registry	107-21-1	57-55-6
NIOSH RTECS	KW2975000	TY2000000
EPA hazardous waste	No data	No data
OHM/TADS	7216718[e]	7216877
DOT/UN/NA/IMCO shipping	No data	No data
HSDB	5012	174
NCI	C00920	No data

[a]Unless otherwise noted, all references for Ethylene glycol are HSDB 1994a.
[b]Unless otherwise noted, all references for Propylene glycol are HSDB 1994b.
[c]Ovrebo et al. 1987
[d]EPA 1987a
[e]OHM/TADS 1985

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 3-2. Physical and Chemical Properties of Ethylene Glycol and Propylene Glycol

Property	Ethylene glycol[a]	Propylene glycol[b]
Molecular weight	62.07[c,d]	76.11[c]
Color	Clear, colorless[f]	Colorless[e]
Physical state	Liquid[c]	Liquid[c]
Melting point	–11.5 °C[d]	–60 °C[f,c] (forms glass)
Boiling point	198 °C[d]	187.6 °C; 188.2 °C[c]
Density:		
at 20 °C (g/cm^3)	1.1135[c]	1.0361[d]
at 30 °C (g/cm^3)	1.1065[c]	No data
Odor	Odorless	Odorless
Odor threshold	No data	No data
Solubility: water at 20 °C	Miscible with water	Miscible with water
Organic solvent(s)	Soluble in lower aliphatic alcohols, glycerol, acetic acid, acetone[c]; Slightly soluble in ether; practically insoluble in benzene, chlorinated hydrocarbons, petroleum ether, oils	Soluble in alcohol, ether, benzene; soluble in acetone, chloroform[c]
Partition coefficients:		
Log K_{ow}	–1.36	–0.92[g,h]
Log K_{oc}	0.592[f]	0.88[f], 0.76[h]
Vapor pressure at 20 °C	0.06 mm Hg	0.07 mm Hg[also e]
Henry's law constant: at 25 °C	2.34×10^{-10} atm-m^3/mole	1.2×10^{-8} atm-m^3/mole 1.7×10^{-8} atm-m^3/mole[h]
Autoignition temperature	412.93 °C[i] 398 °C[j]	421.26 °C[i] 371 °C[j]
Flashpoint	111.26 °C[i,j]	99.04 °C[i,j]
Flammability limits	3.2–21.6%[i,j]	2.6–12.5%[i,j]
Conversion factors	1 ppm = 2.54 mg/m^3 [k] 1 mg/L = 365.0 ppm[k]	1 ppm = 3.11 mg/m^3 [k] 1 mg/L = 321.6 ppm[k]
Explosive limits	No data	No data

[a]Unless otherwise noted all references for ethylene glycol are HSDB 1995a.
[b]Unless otherwise noted all references for propylene glycol are HSDB 1995b.
[c]Merck 1989
[d]Weast 1988
[e]Lewis 1993
[f]Daubert and Danner 1980
[g]EPA 1987a
[h]ASTER 1995
[i]Daubert and Danner 1989
[j]NFPA 1994
[k]Rowe and Wolf 1982

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Historically, ethylene glycol has been commercially produced on a large scale by hydration of ethylene oxide (Merck 1989). Currently, it is also produced by the oxidation of ethylene in the presence of acetic acid to form ethylene diacetate which is then hydrolyzed to the glycol, with the acetic acid recycled in the process (Rowe and Wolf 1982). Ethylene glycol was ranked 30th on a list of the top 50 chemicals produced in the United States in both 1992 and 1993 (Chemical and Engineering News 1994).

The companies that produce ethylene glycol in the United States, their production sites, and the annual capacities in millions of pounds for 1993 (the most recent year for which figures are available) are shown below (SRI 1993).

Company	Annual Production	Site Capacity
BASF Corporation	Geismar, LA	470
Dow Chemical	Plaquemine, LA	450
Eastman Chemical Company	Longview, TX	230
Hoechst Celanese Group Corp.	Clear Lake, TX	550
Occidental Petroleum Corp.	Bayport, TX	580
PD Glycol	Beaumont, TX	790
Quantum Chemical Corp.	Morris, IL	220
Shell Oil Company	Geismar, LA	525
Sun Company, Inc.	Brandenburg, KY	2
Texaco Chemical Company	Port Neches, TX	735
Union Carbide Corporation	Seadrift, TX	550
	Taft, LA	1,400
Total Production		**6,502**

Over the past several years, production volume of ethylene glycol has remained relatively constant at a level of approximately 6,000 million pounds per year (SRI 1989, 1991, 1993). The production volumes were 5,925, 6,250, and 6,502 million pounds in 1989, 1991, and 1993, respectively.

A list of ethylene glycol production and processing facilities in the United States in 1993 is given in Table 4-1. Table 4-1 lists the number of facilities in each state that manufacture or process ethylene glycol, the range of maximum amounts of ethylene glycol that are stored on-site, and the intended use. The data presented in Table 4-1 are from the Toxic Release Inventory (TRI93 1995). Data from this table should be used with caution since only certain types of facilities are required to report (EPA 1995c). This is not an exhaustive list.

Propylene glycol is produced commercially from the hydration of propylene oxide (Merck 1989). Propylene glycol also is produced by the liquid-phase high pressure reaction (600 atmospheres) of synthetic gas in the presence of a rhodium cluster complex (Kirk-Othmer Encyclopedia of Chemical Technology 1978).

The companies that produce propylene glycol in the United States, their production sites, and the annual capacities in millions of pounds for 1993 (the most recent year for which figures are available) are shown below (SRI 1993).

Company	Production Site	Capacity
ARCO Chemical Company	Bayport, TX	374
Dow Chemical USA	Freeport, TX	250
	Plaquemine, LA	150
Eastman Chemical Company	South Charleston, WV	72
Olin Corporation	Brandenburg, KY	70
Texaco Chemical Company	Port Neches, TX	120
Total Production		**1,036**

Over the past few years, production of propylene glycol has remained relatively constant at a level of approximately 1,000 million pounds per year (SRI 1989, 1991, 1993, 1995). The production volumes were 935, 1,000, 980, and 1,036 million pounds in 1989, 1991, 1993, and 1995, respectively.

There is no information on facilities that manufacture or process propylene glycol in the United States available in the Toxic Release Inventory because information on this chemical is not required to be reported (EPA 1995c).

Table 4-1. Facilities That Manufacture or Process Ethylene Glycol

State[a]	Number of facilities	Range of maximum amounts on-site in thousands of pounds[b]	Activities and uses[c]
AK	1	10-100	13
AL	16	0-10000	1, 6, 7, 8, 11, 12, 13
AR	17	1-50000	1, 2, 4, 5, 7, 8, 9, 11, 12, 13
AZ	8	0-100	1, 2, 3, 5, 8, 12, 13
CA	85	0-50000	2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13
CO	8	1-10000	1, 5, 7, 8, 10, 12, 13
CT	9	1-100	1, 5, 7, 8, 9, 12, 13
DE	10	0-1000	1, 5, 6, 7, 8, 9, 11, 12, 13
FL	30	1-1000	2, 4, 7, 8, 9, 11, 12, 13
GA	51	0-1000	1, 2, 3, 5, 7, 8, 9, 10, 11, 12, 13
IA	18	1-10000	1, 2, 3, 5, 8, 9, 10, 11, 12, 13
ID	4	1-1000	1, 5, 8, 11, 12
IL	98	0-50000	1, 2, 4, 5, 7, 8, 9, 10, 11, 12, 13
IN	48	0-10000	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13
KS	12	0-1000	1, 5, 8, 9, 10, 11, 12, 13
KY	36	0-10000	1, 4, 5, 7, 8, 9, 10, 11, 12, 13
LA	32	0-50000	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13
MA	17	0-1000	1, 2, 3, 8, 9, 11, 12, 13
MD	17	1-1000	1, 5, 7, 8, 9, 10, 11, 12, 13
ME	10	1-1000	8, 10, 11, 12, 13
MI	52	0-500000	1, 3, 7, 8, 9, 10, 11, 12, 13
MN	16	0-10000	1, 5, 7, 8, 9, 10, 12, 13
MO	32	1-50000	7, 8, 9, 10, 11, 12, 13
MS	10	1-1000	1, 5, 7, 8, 11, 12, 13
MT	4	10-1000	8, 12, 13
NC	52	0-50000	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
ND	4	1-100	9
NE	8	1-10000	8, 9, 12, 13
NH	5	1-100	1, 5, 8, 9, 10, 11, 13
NJ	59	1-10000	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13
NM	4	1-100	8, 10, 12, 13
NV	1	10-100	8
NY	35	0-1000	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13
OH	93	0-100000	1, 2, 4, 5, 7, 8, 9, 10, 11, 12, 13
OK	13	1-10000	7, 8, 9, 10, 12, 13
OR	12	0-1000	7, 8, 9, 10, 12, 13
PA	56	1-50000	1, 2, 3, 5, 7, 8, 9, 10, 11, 12, 13
PR	18	1-1000	1, 2, 3, 5, 7, 8, 9, 11, 12, 13
RI	7	1-10000	1, 2, 4, 5, 7, 8, 10, 11, 12, 13
SC	54	0-50000	1, 5, 7, 8, 9, 10, 11, 12, 13
TN	36	0-50000	1, 2, 3, 5, 7, 8, 9, 10, 11, 12, 13
TX	106	0-100000	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
UT	6	1-1000	2, 5, 7, 8, 10, 12, 13
VA	25	0-10000	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13

Table 4-1. Facilities That Manufacture or Process Ethylene Glycol (continued)

State[a]	Number of facilities	Range of maximum amounts on-site in thousands of pounds [b]	Activities and uses [c]
WA	14	0-100	8, 9, 10, 11, 12, 13
WI	32	0-10000	8, 9, 10, 11, 12, 13
WV	12	1-100000	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
WY	3	1-100	2, 3, 8, 11, 12

Source: TRI93 1995

[a] Post office state abbreviations used
[b] Data in TRI are maximum amounts on-site at each facility
[c] Activities/Uses:

1. Produce
2. Import
3. For on-site use/processing
4. For sale/distribution
5. As a by-product
6. As an impurity
7. As a reactant
8. As a formulation component
9. As a product component
10. For repackaging
11. As a chemical processing aid
12. As a manufacturing aid
13. Ancillary or other uses

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.2. IMPORT/EXPORT

Ethylene glycol has been imported into the United States in large quantities over the last several years. Import volume since 1992 has averaged 200 million kg per year (440 million pounds per year). Import volume was 180,213,702 kg (397 million pounds) in 1992; 171,087,963 kg (377 million pounds) in 1993; and 239,109,749 kg (527 million pounds) in 1994 (NT.DB 1995).

Ethylene glycol also has been exported in large quantities over the last several years with export volume generally being twice that of the import volume for any given year. Export volume since 1990 has averaged 415 million kg per year (915 million pounds per year). Export volume for ethylene glycol was 390,056,362 kg (869 million pounds), 413,797,808 kg (912 million pounds), 396,227,465 kg (874 million pounds), 452,126,142 kg (997 million pounds), and 423,179,712 kg (933 million pounds) in 1990, 1991, 1992, 1993, and 1994 respectively (NTDB 1995).

Propylene glycol has been imported into the United States in ever increasing quantities over the last several years. Import volume increased from 198,031 kg (0.4 million pounds) in 1992, to 2,167,664 kg (4.8 million pounds) in 1993, to 5,249,265 kg (11.6 million pounds) in 1994 (NTDB 1995).

Propylene glycol also has been exported over the last several years with export volume greatly exceeding the import volume in any given year. Export volume for propylene glycol has declined slightly since 1990, but has averaged 77,000,000 kg per year (170 million pounds per year). Export volumes for propylene glycol were 94,606,830 kg (209 million pounds), 64,850,502 kg (143 million pounds), 62,940,802 kg (139 million pounds), 81,531,357 kg (180 million pounds), and 78,997,747 kg (174 million pounds) in 1990, 1991, 1992, 1993, and 1994, respectively (NTDB 1995).

4.3 USE

Ethylene glycol has been used extensively in many different industrial applications because of its chemical and physical properties. Ethylene glycol dissolves in water and is miscible in alcohol and acetone, has the capacity to hold large amounts of heat before boiling, and lowers the freezing point of water (Lewis 1993). In addition, ethylene glycol is hygroscopic (has the ability to absorb twice its weight in water), is suitable for use as an industrial humectant (drying agent), and possesses excellent

solvent properties (Lewis 1993; Merck 1989; Rowe and Wolf 1982). Approximately 39% of all ethylene glycol produced is used to make antifreeze, 29% is used to make polyester fibers, 26% is exported, and 23% is used to make polyethylene terephthalate (PET) bottles, films, resin products, and in other miscellaneous industrial applications (HSDB 1995a).

The major use of ethylene glycol is in the transportation industry, where it has been used as an ingredient in hydraulic brake fluids, as the major component in automotive antifreeze/coolant, and as a component of de-icing fluids for aircraft, runways, and taxiways (Klecka et al. 1993; Lewis 1993; Merck 1989; Rowe and Wolf 1982). Ethylene glycol also has been used as an intermediate in the synthesis of esters, ethers, and resinous products, particularly polyester fibers (Terylene, Dacron) and resins, and as a solvent (Merck 1989; Rowe and Wolf 1982). As a solvent, ethylene glycol has been used in the paint and plastic industries in the formulation of printers' inks, stamp pad inks, and inks for ball point pens, and as a softening agent in cellophane (Merck 1989; Rowe and Wolf 1982). Ethylene glycol is also used as a stabilizer for soy bean foam used in fire extinguishers, in photographic developing solutions, and in the manufacture of explosives, plasticizers, elastomers, and synthetic waxes (Lewis 1993; Merck 1989). Small amounts of ethylene glycol are used in pharmaceutical preparations (components of skin lotions, powders, and as a substitute for glycerin) (Browning 1965) and as a preservative in pitfall traps for sampling beetles and other surface-active soil arthropods (Holopainen 1992).

Like ethylene glycol, propylene glycol has been used extensively in many different industrial applications because of its chemical and physical properties. Propylene glycol dissolves in water and is miscible with alcohol, acetone, chloroform, and other organic solvents; has the capacity to hold large amounts of heat before boiling; and lowers the freezing point of water (EPA 1987a; Lewis 1993). In addition, propylene glycol is hygroscopic, is suitable for use as an industrial humectant, and possesses excellent solvent properties (Lewis 1993; Merck 1989; Rowe and Wolf 1982). Approximately 41% of all propylene glycol produced is used for unsaturated polyester resin production, 29% is exported, 11% is used in foods, pharmaceutical products, and cosmetics, 7% is used in semi-moist pet food, 4% is used as a humectant for tobacco, 4% is used in functional fluids, and 4% is for miscellaneous uses (HSDB 1995b).

The major use of propylene glycol is as an intermediate in the manufacture of cross-linked polyesters and hydroxylated polyester resins. In the airline industry, ethylene glycol has been used as a base

component of de-icing fluids for aircraft, runways, and taxiways (Klecka et al. 1993; Kirk-Othmer Encyclopedia of Chemical Technology 1978). Propylene glycol is a solvent and humectant for various pharmaceuticals, hair colorant formulations, and food and tobacco products (Kirk-Othmer Encyclopedia of Chemical Technology 1978; Merck 1989). In addition, the use of small amounts of propylene glycol is permitted in foods as an anticaking agent, antioxidant, dough strengthener, emulsifier, processing aid, stabilizer and thickener, surface active agent or texturizer (EPA 1979). In veterinary medicine, propylene glycol is used in oral medications for ruminants and as a solvent for various drugs (Merck 1983). As a nontoxic antifreeze, propylene glycol is used in breweries and dairy establishments and as an inhibitor of fermentation and mold growth (Merck 1989). The chemical has been used as an emollient in pharmaceutical and cosmetic creams because it readily absorbs water. Propylene glycol has even been used in vapor form as an air sterilizer in hospitals and public buildings, and in veterinary applications to protect animals against the spread of airborne bacteria and influenza virus (Kirk-Othmer Encyclopedia of Chemical Technology 1978; Rowe and Wolf 1982). Used as a mist, propylene glycol is deployed as a special effect fog/smoke during theatrical performances, rock concerts, private parties, and in fire training programs to simulate fire fighting conditions (Ross01 1993).

4.4 DISPOSAL

Ethylene glycol is listed as a toxic substance under Section 313 of the Emergency Planning and Community Right-to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (EPA 1995).

Two promising methods for the complete (>99%) destruction of ethylene glycol in waste water are ultraviolet (UV) light-catalyzed oxidation and supercritical oxidation. In the UV light-catalyzed oxidation method, ethylene glycol-containing waste water in the presence of 10% hydrogen peroxide is oxidized by UV irradiation (200-250 nm) with light from a mercury lamp (Wang et al. 1993). The W/hydrogen peroxide undergoes photochemical decomposition to produce OH radicals that are strong oxidants capable of oxidizing most organic compounds stepwise to complete mineralization (e.g., carbon dioxide and water). In the supercritical water oxidation method, the waste water is subjected to oxidation at >550 °C and 4,000 psi pressure with a residence time of <30 seconds (Rice et al. 1993).

A new technology, in situ vitrification (a thermal treatment technology) (Drajun 1991) has shown potential for the remediation of soil contaminated with ethylene glycol. During the *in situ* vitrification process, contaminated soil is transformed into silicate glass using large amounts of electrical energy and a crystalline product similar to obsidian is formed. Another novel approach involving an encapsulated biooxidation method proposes that sodium percarbonate encapsulated in polyvinylidene chloride be inserted in subsurface soil by a method called hydraulic fracturing. Oxygen slowly released from the encapsulated sodium percarbonate increases the number of glycol-degrading organisms. This method is expected to remediate soils contaminated with glycols via enhanced aerobic biodegradation in subsurface soils (Vesper et al. 1994).

Distillation of used automobile and heavy duty engine coolant under reduced pressure has been assessed to be an acceptable technology for recycling ethylene glycol in terms of economic potential, waste reduction potential, and product quality that meets both American Society for Testing and Materials (ASTM) and SAE standards (Randall and Gavaskar 1993).

Propylene glycol is currently listed as a Generally Recognized as Safe (GRAS) additive in foods (FDA 1982) and is not listed as a toxic substance under Section 313 of the Emergency Planning and Community Right-to Know Act under Title III of the Superfund Amendments and Reauthorization Act (EPA 1995c).

Two methods for treatment of waste water containing propylene glycol include a methane fermentation process and a newly developed biotreatment process that uses mixed cultures of bacteria to degrade the compound. The methane fermentation process has proven to be a reliable as well as cost and energy efficient method for the treatment of domestic sludges and certain industrial waste water containing propylene glycol and other organic compounds (Chou et al. 1979). Propylene glycol in effluents from propylene oxide production plants contains both high biological oxygen demand/chemical oxygen demand (BOD/COD) loads and high chloride concentrations. The high salinity poses problems to waste water treatment such as activated sludge and activated carbon absorption processes A novel and economically viable propylene glycol biotreatment process recently has been developed that uses a mixed culture of engineered bacterial species from the genera *Pseudomonas* and *Aerobacter*. *The Pseudomonas* use propylene glycol to produce volatile acids, while *Aerobacter* were effective in degrading the volatile acids to carbon dioxide and water (Raja et al. 1991).

A new encapsulated biooxidation method has shown potential for the remediation of soil contaminated with propylene glycol (Vesper et al. 1994). The encapsulated biooxidation method proposes that sodium percarbonate encapsulated in polyvinylidene chloride be inserted in subsurface soil by a method called hydraulic fracturing. Oxygen slowly released from the encapsulated sodium percarbonate increases the number of glycol-degrading organisms. In a laboratory experiment conducted over a 30-day period at 12 °C that simulated subsurface soil temperatures, the concentration of propylene glycol was reduced lo-fold and the number of propylene glycol degrading organisms increases 10-fold compared to live controls without the encapsulated sodium percarbonate. This method is expected to remediate soils contaminated with glycols via enhanced aerobic biodegradation in subsurface soils. The hydraulic fracturing technique that would be used to deliver the encapsulated sodium percarbonate to the subsurface soils involves creating horizontal pancake-shaped fractures that are 5 meters in diameter and l-2 cm in thickness. These fractures are stacked vertically in the subsoil, and granular material is injected into each fracture (Vesper et al. 1994). The advantage of this method is that oxygen can be delivered deep into contaminated subsurface soil and then made available slowly to stimulate bacterial growth.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

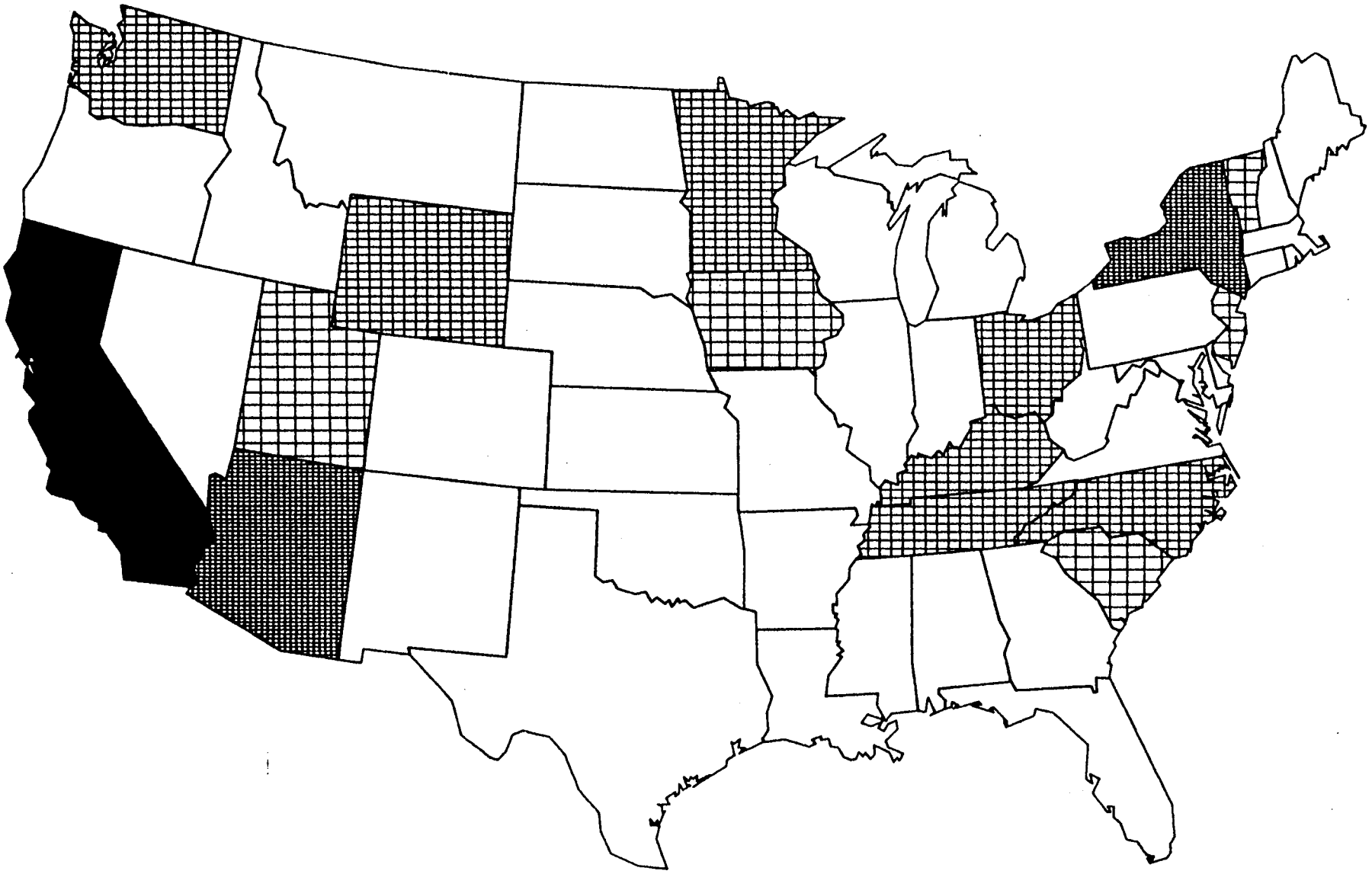
Ethylene glycol is released to the environment in manufacturing and processing waste streams and as the result of disposal of industrial and consumer products containing this compound. The major sources of releases are from the disposal of used antifreeze and de-icing solutions. Upon release to the environment, the compound is expected to partition to and be transported in surface water and groundwater. Because of its high solubility in water and lack of adsorption or partitioning into soils, ethylene glycol will have a high mobility in soil and potential to leach into groundwater. Ethylene glycol is rapidly degraded in all environmental media and it does not persist or bioaccumulate. Biodegradation is the most important transformation process in surface waters and soils. Assuming first order kinetics, the half-life for ethylene glycol in water is estimated to be 2-12 days under aerobic and 8-48 days under anaerobic conditions while the half-life in soil is estimated to be 0.2-0.9 days. Aerosols or vapors released to the atmosphere readily undergo photochemical oxidation with an estimated half-life of 0.3-3.5 days. Little information was found on concentrations of ethylene glycol in any environmental media.

The most important routes of exposure to ethylene glycol for members of the general population are dermal contact with products containing this compound (antifreeze and hydraulic fluids) and intentional or accidental oral exposures. In occupational settings, workers are exposed via dermal and possibly inhalation contact in applications involving the heating or spray application of fluids containing this compound.

Ethylene glycol has been identified in at least 34 of 1,416 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 1995). However, the number of sites evaluated for ethylene glycol is not known. The frequency of these sites within the United States can be seen in Figure 5-1.

Propylene glycol is released to the environment in manufacturing and processing waste streams and as the result of disposal of industrial and consumer products containing this compound. The major sources of releases are from the use and disposal of this compound in de-icing solutions. Because of its solubility in water and lack of adsorption and partitioning to soils, propylene glycol will have a

FIGURE 5-1. FREQUENCY OF NPL SITES WITH ETHYLENE GLYCOL CONTAMINATION *



*Derived from HazDat 1995

high mobility in soil and potential to leach into groundwater. Upon release to the environment, the compound is expected to partition to and be transported in surface water and groundwater. Propylene glycol is rapidly degraded in all environmental media; it is not expected to persist or bioaccumulate in aquatic organisms. Biodegradation is the most important transformation process in surface waters and soils. Assuming first order kinetics, the half-life of propylene glycol in water is estimated to be l-4 days under aerobic and 3-5 days under anaerobic conditions. The half-life of propylene glycol in soil is expected to be equal to or slightly less than that for water. Vapors released to the atmosphere readily undergo rapid photochemical oxidation via reaction with hydroxyl radicals with an estimated half-life of 0.8 days. Little information was found on concentrations of this compound in any environmental media. Propylene glycol is a Generally Recognized as Safe (GRAS) food additive that is widely used in food and tobacco products, pharmaceuticals, and cosmetics.

The most important routes of exposure to propylene glycol for members of the general population are ingestion and dermal contact with products containing this compound. The general public also may be exposed to small amounts of propylene glycol released from newly installed carpet with polyvinyl backing. In occupational settings, workers are exposed via dermal contact and possibly inhalation in applications involving the heating or spray application of fluids containing this compound.

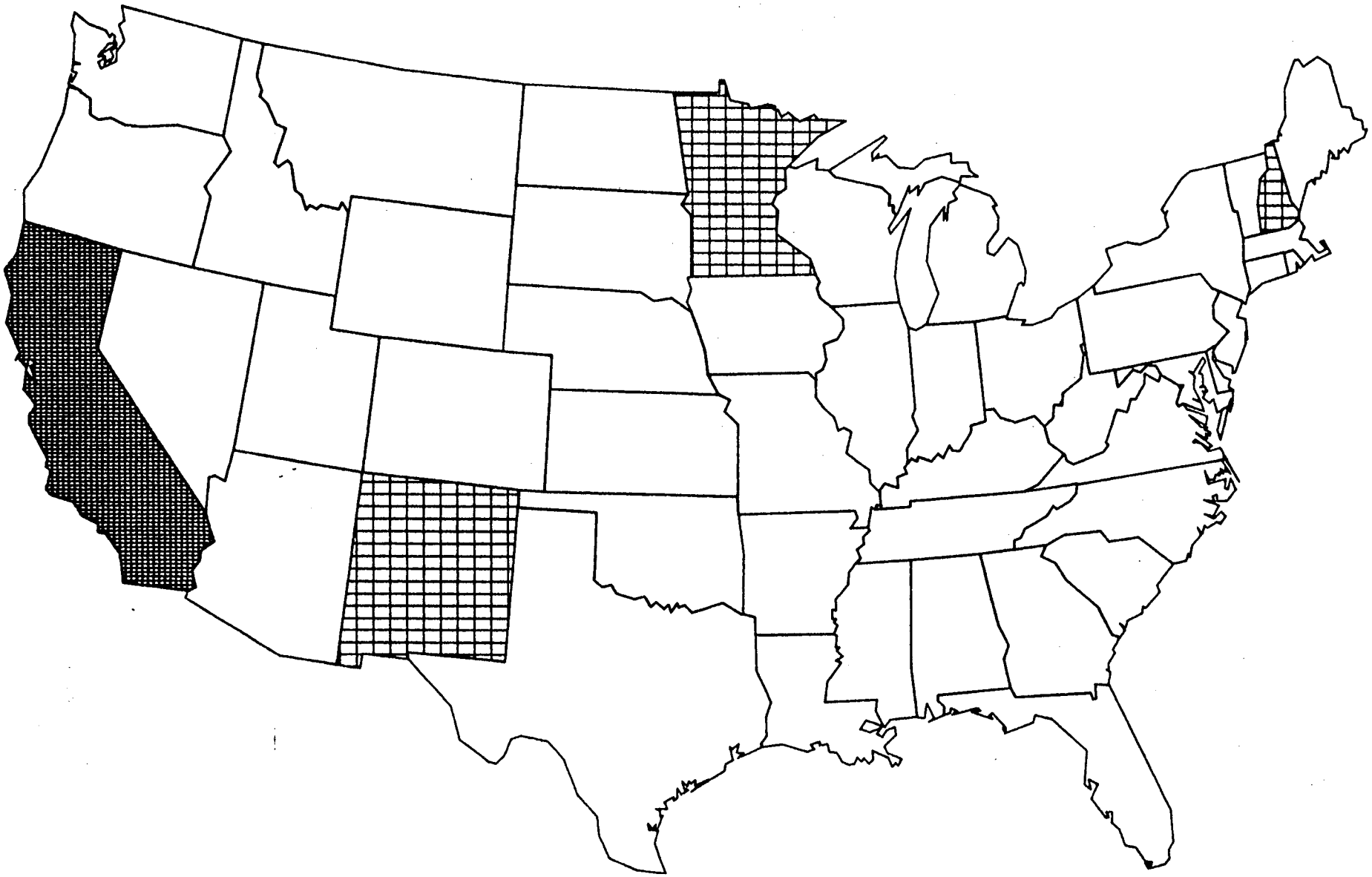
Propylene glycol has been identified in at least 5 of 1,416 hazardous waste sites that have been proposed for inclusion on the EPA NPL (HazDat 1995). However, the number of sites evaluated for propylene glycol is not known. The frequency of these sites within the United States can be seen in Figure 5-2.

5.2 RELEASES TO THE ENVIRONMENT

Releases of ethylene glycol are required to be reported under SARA Section 313; consequently data are available for this compound in the 1993 Toxic Release Inventory (EPA 1995c). There are at least 34 NPL hazardous waste site where ethylene glycol has been identified in some environmental media (HazDat 1995).

Releases of propylene glycol are not required to be reported under SARA Section 313; consequently there are no data for this compound in the 1993 Toxic Release Inventory (EPA 1995c). There are at

FIGURE 5–2. FREQUENCY OF NPL SITES WITH PROPYLENE GLYCOL CONTAMINATION *



*Derived from HazDat 1995

least 5 NPL hazardous waste site where propylene glycol has been identified in some environmental media (HazDat 1995).

5.2.1 Air

The estimated releases of 10 million pounds of ethylene glycol to the atmosphere accounted for about 55% of the estimated total environmental releases from 1,296 domestic manufacturing and processing facilities in 1993 (TR193 1995). These releases are summarized in Table 5-l. On a nationwide basis, the total amount of ethylene glycol released to the atmosphere appears to have changed very little during the period 1990-93 (as shown in Table 5-2). The data from the Toxic Release Inventory (TRI) listed in Tables 5-l and 5-2 should be used with caution, however, since only certain types of facilities are required to report (EPA 1995c). This is not an exhaustive list.

Ethylene glycol has been detected in air samples collected at four hazardous waste sites where it was detected in some environmental media (HazDat 1995). During the application of de-icing solutions to aircraft, an estimated 49-80% of de-icing solutions containing both ethylene glycol and propylene glycol are released on airport runway aprons. The remainder is retained on the aircraft or is immediately dispersed to the air (Sills and Blakeslee 1992); however, releases to the atmosphere are limited by its low vapor pressure (Ware 1988).

Little information was found regarding the release of propylene glycol to the atmosphere. Propylene glycol used as a solvent in paints, inks, and coatings will slowly volatilize to the atmosphere (EPA 1987a). During the application of de-icing solutions to aircraft, an estimated 49-80% of de-icing solutions containing both ethylene glycol and propylene glycol are released on airport runway aprons. The remainder is retained on the aircraft or is immediately dispersed to the air (Sills and Blakeslee 1992); however, release to the atmosphere is expected to be limited by the compound’s low vapor pressure.

There is no information on releases of propylene glycol to the atmosphere from domestic manufacturing and processing facilities because these releases are not required to be reported (EPA 1995c). Propylene glycol has not been detected in air samples collected at any hazardous waste sites where it was detected in some environmental media (HazDat 1995).

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Ethylene Glycol

State[b]	Number of facilities	Range of reported amounts released in pounds per year[a]						
		Air	Water	Land	Underground injection	Total environment[c]	POTW transfer	Off-site waste transfer
AK	1	250	8000	5	0	8255	0	0
AL	16	0-157000	0-4200	0-1400	0	0-157000	0-1246	0-30130
AR	17	0-28552	0-660	0	0	0-28552	0-1300	0-170000
AZ	8	0-765	0	0	0	0-765	0-75000	0-90900
CA	85	0-17005	0-178204	0-28545	0-1393	0-178204	0-178204	0-270000
CO	8	0-281	0-1700	0	0	0-1717	0-33000	0-119815
CT	9	0-2200	0-16400	0	0	0-16400	0-1600	0-4530
DE	10	0-111	0-82	0	0	0-111	0-27789	0-22000
FL	30	0-68000	0-1521	0-5200	0-750	0-68000	0-21000	0-26950
GA	51	0-35329	0-7900	0-1000	0	0-35329	0-69000	0-1307215
IA	18	0-3198	0-60	0	0	0-3198	0-4438600	0-38990
ID	4	0-42000	0	0	0	0-42000	0-29600	0-18700
IL	98	0-49000	0-22000	0-5300	0	0-54610	0-57500	0-136743
IN	48	0-19040	0-234098	0-17199	0	0-234098	0-48000	0-16446044
KS	12	0-34320	0-20000	0	0	0-54320	0-15000	0-135262
KY	36	0-33000	0-25206	0-13623	0	0-33000	0-8500	0-87000
LA	32	0-194000	0-32000	0-447		0-266218	0-750	0-37859
MA	17	0-10470	0-4565	0	0	0-10470	0-84493	0-42581
MD	17	0-72900	0-9	0	0	0-72900	0-40400	0-150958
ME	10	0-10981	0-5200	0-240523	0	0-251504	0-12500	0-23016
MI	52	0-18000	0-5400	0-410	0-750	0-18000	0-72200	0-144600
MN	16	0-24170	0-3300	0	0	0-24170	0-250000	0-13539
MO	32	0-12000	0-35	0-400	0	0-12000	0-39000	0-73300
MS	10	0-2000	0-43000	0-5	0	9-45000	0-5	0-140000
MT	4	0-500	0-9500	0	0	0-9530	0	0-250
NC	52	0-380000	0-13192	0-3100	0	0-380025	0-41700	0-29602040
ND	4	0-250	0	0	0	0-250	0-620	0-1500
NE	8	0-500	0-250	0-250	0	0-500	0-750	0-750
NH	5	0-1800	0	0	0	0-1800	0-9300	0-15000
NJ	59	0-5723	0-529	0	0	0-5723	0-1224297	0-82954

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Ethylene Glycol

State[b]	Number of facilities	Range of reported amounts released in pounds per year[a]						
		Air	Water	Land	Underground injection	Total environment[c]	POTW transfer	Off-site waste transfer
NM	4	220-2521	0	0-200	0	420-2521	0-184530	0-64549
NV	1	10	0	0	0	10	0	0
NY	35	0-20760	0-8840	0-250	0	0-20760	0-55000	0-59250
OH	93	0-189327	0-152022	0-39000	0	0-189327	0-79000	0-217000
OK	13	0-18000	0	0-250	0	0-18000	0-13900	0-8379
OR	12	0-22400	0-750	0	0	0-22400	0-120000	0-1700
PA	56	0-69539	0-24000	0-250	0	0-69539	0-13819	0-130417
PR	18	0-10200	0	0-250	0	0-10200	0-17452	0-126000
RI	7	0-15472	0-19964	0	0	0-21356	0-12400	0-3827459
SC	54	0-185000	0-11789	0-2400	0	0-185140	0-104250	0-30971777
TN	36	0-131000	0-75000	0-225000	0	0-232255	0-77000	0-200000
TX	106	0-3165000	0-7700	0-57000		0-8765000	0-1131000	0-2423611
UT	6	0-3147	0	0-17550	0	0-17550	0-47537	0
VA	25	0-496479	0-1338	0-250	0	0-496479	0-1565885	0-4548200
WA	14	0-5262	0	0	0	0-5262	0-250	0-8673
WI	32	0-77500	0-4530	0-600000	0	0-600000	0-62400	0-70750
WV	12	0-1350422	0-19846	0-457	0	3-1350925	0-110230	0-10252484
WY	3	0-74	0	0	0-18966	72-18966	0	0-1104

Source: TRI93 1995

POTW = Publicly owned treatment works

[a] Data in TRI are maximum amounts released by each facility.

[b] Post office state abbreviations used

[c] The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility

Table 5-2. National Ethylene Glycol Emissions in Pounds per Year in Different Environmental Media During 1990–1993

Medium	Year			
	1990	1991	1992	1993
Air	10,970,217	10,803,502	10,251,162	10,224,243
Water	2,754,760	2,313,490	1,326,208	1,162,522
Underground injection	5,809,297	3,654,273	4,923,321	5,943,528
Land	987,625	908,417	908,417	1,282,769
Total emissions	20,521,899	17,679,682	17,185,279	18,613,062
POTW	15,958,825	19,321,608	19,775,302	15,062,080
Offsite	11,284,651	102,777,473	117,787,794	133,894,430

Source: TRI90 1992; TRI91 1993; TRI92 1994; TRI93 1995
POTW = Publicly owned treatment works

5.2.2 Water

Ethylene glycol is released to surface waters in waste water from production and processing facilities, from spills, in runoff (e.g., through the use of the compounds as de-icing fluids), and in the disposal of used antifreeze (Ware 1988). Ethylene glycol concentrations up to 19,000 mg/L (ppm) were detected in storm water runoff at the Salt Lake City Airport in Utah, and airport runoff was found to contain up to 3,100 mg/L (ppm) at the Toronto International Airport in Canada and up to 5,050 mg/L (ppm) at the Denver Airport in Colorado (Sills and Blakeslee 1992). Ethylene glycol was detected, but the concentration was not quantified in effluents from a chemical plant in Brandenburg, Kentucky (EPA 1976).

According to the Toxics Release Inventory (TRI), an estimated 1.2 million pounds of ethylene glycol were released to surface waters in 1993 from 1,296 domestic manufacturing and processing facilities accounting for 6% of the estimated total environmental releases (TR193 1995). An additional 15 million pounds were released in effluents to publicly owned treatment works (POTW) (TR193 1995). During the period 1990-93, the nationwide release of ethylene glycol to surface water from manufacturing and processing facilities appears to have declined significantly (by more than 50%) from 2.8 million pounds in 1990 to 1.2 million pounds in 1993, while the trend in the total discharge to POTWs during the same period appears to have remained relatively constant with slightly higher discharges (approximately 20 million pounds) being sent to POTWs in 1991 and 1992 (see Table 5-2). As a result of secondary treatment processes in POTWs, only a small portion (0-12%) of the ethylene glycol that enters POTWs is subsequently released to surface waters (Howard et al. 1991).

Groundwater samples collected from a perched water table at the Ottawa Airport in Canada contained 415 mg/L (ppm) of ethylene glycol (Sills and Blakeslee 1992). Ethylene glycol also has been detected in groundwater samples collected at 7 hazardous waste sites where it was detected in some environmental media (HazDat 1995).

Propylene glycol is released to surface waters in waste water from production and processing facilities and from spills and in runoff (e.g., through the use of the compound in de-icing fluids). Propylene glycol concentrations up to 19,000 mg/L (ppm) were detected in storm water runoff at the Salt Lake City Airport in Utah (Sills and Blakeslee 1992). Propylene glycol was detected, but the concentration was not quantified in effluents from a chemical manufacturing plant in Memphis, Tennessee (EPA

1976). Propylene glycol may also be released to surface waters as a metabolite of propylene glycol dinitrate which is a military propellant found in waste water streams from munitions facilities (EPA 1979, 1987a; Kaplan et al. 1982; Walker and Kaplan 1992, 1992).

There is no information in the Toxic Release Inventory (TRI) on releases of propylene glycol to surface or groundwater from domestic manufacturing and processing facilities because these releases are not required to be reported (EPA 1995c).

Groundwater samples collected from a perched water table at the Ottawa Airport in Canada contained 4 mg/L (ppm) of propylene glycol (Sills and Blakeslee 1992). Propylene glycol also has been detected in groundwater samples collected at two hazardous waste sites where it was detected in various environmental media (HazDat 1995).

5.2.3 Soil

The major sources of ethylene glycol releases to soil are from the disposal of used antifreeze fluids and de-icing fluids containing the compound (EPA 1979, 1987a; Ware 1988). Smaller amounts of ethylene glycol are released to soil from the disposal of vehicular hydraulic brake fluids (EPA 1979, 1987a). Ethylene glycol may also be released to soil via natural processes associated with the metabolism of ethylene by plants (Blomstrom and Beyer 1980).

According to TRI, an estimated total of 1.3 million pounds of ethylene glycol was released to soils from 1,296 domestic manufacturing and processing facilities accounting for almost 7% of total environmental releases in 1993 (TRI93 1995). An additional 5.9 million pounds, constituting about 32% of the total environmental emissions, were released by underground injection (TR193 1995). Nationwide release data for the period from 1990 to 1993, shown in Table 5-2, indicate that the amount of ethylene glycol released to land has fluctuated greatly. The amount of ethylene glycol released via underground injection has also fluctuated during this period with higher releases reported in 1990 and 1993 and significantly lower releases in both 1991 and 1992.

Ethylene glycol has been detected (at an unspecified concentration) in a soil sample collected at an NPL hazardous waste site where it was detected in various environmental media (HazDat 1995).

The major sources of propylene glycol releases to soil are the disposal of used antifreeze fluids and de-icing fluids containing the compounds (EPA 1979, 1987a).

There is no information in the TRI on releases of propylene glycol to soil from domestic manufacturing and processing facilities because these releases are not required to be reported (EPA 1995c). Propylene glycol has not been detected in any soil samples collected at hazardous waste sites although it has been detected in other environmental media (HazDat 1995).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Ethylene glycol has a low vapor pressure (0.06 mm Hg at 20 °C) and is miscible with water (see Table 3-2). If released to the atmosphere (e.g., as vapors generated at elevated temperatures), ethylene glycol should exist almost entirely in the vapor phase (Eisenreich et al. 1981). The high solubility of ethylene glycol in water ensures that at least partial removal of the compound will occur by wet deposition. Therefore, upon release to the environment, the compound is expected to be transported primarily in aqueous media (EPA 1979). The low Henry's law constant value for this compound ($2.34x10^{-10}$ atm-m^3/mole; see Table 3-2) suggests that releases to surface water will not partition to the atmosphere via volatilization (Simmons et al. 1976; Thomas 1990). Adsorption to sediment or soil particulates is also not expected to be significant on the basis of the low K_{oc}value (see Table 3-2). Based on the low K_{oc} value (see Table 3-2), ethylene glycol is expected to have a very high mobility in soil and could leach into groundwater (Swann et al. 1983).

The low octanol/water partition coefficient (K_{ow}) values of 0.256 suggests that bioconcentration and biomagnification of ethylene glycol are not likely to occur. Laboratory testing with this compound confirms insignificant bioconcentration in algae and fish (Freitag et al. 1985). The bioconcentration factor (BCF) for ethylene glycol in a fish (Golden ide) was 10 after 3 days of exposure and was 190 after 1 day of exposure in the algae *Chlorella fusca.* The uptake of ethylene glycol by crawfish (Procambarus sp.) was found to be dependent upon the aqueous concentration, but the concentrations in various crayfish tissues were always less than the concentrations in water (Khoury et al. 1993). The BCF in gills, muscle, gastrointestinal tracts, and hepatopancreas of the crawfish were <l even at the highest water concentration. When transferred to freshwater, the depuration of ethylene glycol was

complete in 5 days for crayfish exposed to 50 μg/mL (ppm) and in 6 days for those exposed to 200 and 1,000 μg/mL (ppm) (Khoury et al. 1993).

Ethylene glycol is expected to be highly mobile, particularly in moist soils, and it may leach into groundwater upon release to surface soils. In laboratory studies, ethylene glycol was found to percolate rapidly through soil columns with little or no adsorption (LDOTD 1996; Lokke 1984); however, rapid biodegradation is expected to limit the extent of leaching through soil (see Section 5.3.2.3). The compound may also volatilize from dry surface soils (EPA 1979, 1987a; Hine and Mookerjee 1975). In dry soils, ethylene glycol liquid can enter the soil system and travel through the porous media before contacting free water. Amoozegar et al. (1986) reported that in dry soils (<l% water), however, the rate of ethylene glycol movement was the slowest of 6 organic liquids tested (toluene, xylene, kerosene, acetone, and isopropyl alcohol).

Propylene glycol has a low vapor pressure (0.07 mm Hg at 20 °C) and is miscible with water (see Table 3-2). If released to the atmosphere (e.g., as vapors generated at elevated temperatures), propylene glycol should exist almost entirely in the vapor phase (Eisenreich et al. 1981). The high solubility of propylene glycol in water ensures at least partial removal of the compound will occur by wet deposition (EPA 1987a). Therefore, upon release to the environment, the compound is expected to be transported primarily in aqueous media (EPA 1979). The low Henry's law constant values for the compound ($1.2x10^{-8}$ to $1.7x10^{-8}$ atm-m^3/mole range; see Table 3-2) suggest that releases to surface water will not partition to the atmosphere via volatilization (Simmons et al. 1976; Thomas 1990). Adsorption to sediment or soil particulates is also not expected to be significant on the basis of the low K_{oc} value (see Table 3-2).

Based on the low K_{oc} value, propylene glycol is expected to have a very high mobility in soil and could leach into groundwater (Swann et al. 1983). The low octanol/water partition coefficient (K_{ow}) (see Table 3-2) suggests that bioconcentration and biomagnification are also not likely to occur. No measured BCF values were located for this compound.

Propylene glycol is expected to be highly mobile in moist soils and may leach to groundwater upon release to surface soils; however, rapid biodegradation is expected to limit the extent of the leaching (see Section 5.3.2) (EPA 1987a). The compound may also volatilize from dry surface soils (EPA 1979, 1987a; Hine and Mookerjee 1975).

5.3.2 Transformation and Degradation

5.3.2.1 Air

Ethylene glycol released to the atmosphere is expected to undergo rapid photochemical oxidation via reaction with hydroxyl radicals. The half-life for the photochemical oxidation of ethylene glycol has been estimated to be 8-84 hours (EPA 1987a; Howard et al. 1991).

Propylene glycol released to the atmosphere is expected to undergo rapid photochemical oxidation via reaction with hydroxyl radicals. The half-life for the photochemical oxidation of propylene glycol has been estimated to be 20-32 hours (EPA 1987a; Howard et al. 1990).

5.3.2.2 Water

Biodegradation by a variety of acclimated and unacclimated microorganisms, under both aerobic and anaerobic conditions, is the most important transformation process for ethylene glycol in surface waters. Ethylene glycol is rapidly metabolized in aqueous solutions, as measured using five different biodegradation tests (Means and Anderson 1981). Other reports of biotransformation of ethylene glycol include metabolism by activated or anaerobic sewage sludge microorganisms (Battersby and Wilson 1989; Bieszkiewicz et al. 1979; Dwyer and Tiedje 1983; Watson and Jones 1977), river water microbes (Evans and David 1974), halophilic bacteria (Caskey and Taber 1981; Gonzalez et al. 1972), and pond water microbes (Child and Willetts 1978; Willetts 1981). For example, the biodegradation of ethylene glycol was complete in 3 days at 20 °C and in 14 days at 8 °C when it was added to river water at concentrations ≤10 mg/L (ppm) (Evans and David 1974).

Waste water carrying ethylene glycol could be purified by the activated sludge method providing the concentration of ethylene glycol did not exceed 1,000 mg/L (ppm) (Bieszkiewicz et al. 1979). Similar results were observed for the degradation of ethylene glycol in groundwater (McGahey -arid Bouwer 1992). At an initial substrate concentration of 111 mg/L (ppm), naturally occurring microorganisms in groundwater biodegraded ethylene glycol with an estimated half-life of <l day following a lag phase of <3 days. Increased substrate (ethylene glycol) concentrations decreased the rate of biodegradation. At a substrate concentration of 10,000 mg/L (ppm), however, minimal substrate disappearance was

observed, probably due to oxygen limitation in solution. Howard et al. (1991) estimated a half-life of 2-12 days for ethylene glycol under aerobic conditions and 8-48 days under anaerobic conditions.

Ethylene glycol is not expected to undergo significant abiotic transformation in surface waters via hydrolysis or oxidation (EPA 1979; Harris 1990; Howard et a1.1991). Glycols generally are resistant to hydrolysis (Harris 1990). However, photolysis of ethylene glycol sorbed to goethite (a common natural constituent of surface water sediments) by near ultraviolet radiation (300-400 nm) has been demonstrated in the laboratory. Formaldehyde and glycolaldehyde were detected as degradation products (Cunningham et al. 1985).

Biodegradation by a variety of acclimated and unacclimated microorganisms, under both aerobic and anaerobic conditions, is also the most important transformation process for propylene glycol in surface waters. The half-lives for the biotransformation of propylene glycol generally range from 1 to 4 days under aerobic conditions and from 3 to 5 days under anaerobic conditions (EPA 1987a).

Propylene glycol rapidly disappears from culture flasks containing activated sludge microorganisms under both aerobic and anaerobic conditions (Kaplan et al. 1982). Some propylene glycol was lost from sterile cultures after 9 days. An 8% and 16% loss of propylene glycol was observed in sterile anaerobic and aerobic cultures, respectively. In active cultures, propylene glycol was not detected after 2 days in aerobic nutrient broth. When used as a sole carbon source, propylene glycol disappeared after 4 days under aerobic and 9 days under anaerobic conditions. Raja et al. (1991) reported a novel biotreatment process using *Pseudomonas* and *Aerobacter* bacteria. The *Pseudomonas* were able to use the propylene glycol to produce volatile acids, while *Aerobacter* degraded the volatile acids quickly to carbon dioxide and water.

Propylene glycol is not expected to undergo significant abiotic transformation in surface waters via hydrolysis or oxidation (EPA 1979, 1987a). Glycols generally are resistant to hydrolysis (Harris 1990). For example, the half-life for reaction of propylene glycol with hydroxyl radicals in aqueous solution has been estimated to be 1.3-2.3 years (Harris 1990).

5.3.2.3 Sediment and Soil

Biodegradation by a variety of microorganisms under both aerobic and anaerobic conditions is also the most important transformation process for ethylene glycol in soils, with a half-life similar to or less than that in surface waters (EPA 1987a). In a laboratory study, soil microbes of the genera *Pseudomonas, Citrobacter,* and *Serratia* degraded ethylene glycol, at solution concentrations of 1-3%, within 3 days; concentrations higher than 5% were toxic to the microbes (LDOTD 1990). The soil microbe *Clostridium glycolicum* degraded ethylene glycol under anaerobic conditions to acid and alcohol end products (Gaston and Stadtman 1963).

The rate of biodegradation of ethylene glycol in simulated subsurface soils are dependent on substrate concentrations, soil types, and ambient soil temperatures, but nutritional supplements had minimal effects (McGahey and Bouwer 1992). Greater than 95% removal was consistently accomplished in <5 days and 7 days at ethylene glycol concentrations of 100 ppm and 1,000 ppm, respectively; however, substrate concentrations of 10,000 ppm showed negligible loss of ethylene glycol. Soils with high organic matter, and thus enhanced microbial diversity and activity, also degraded ethylene glycol significantly faster. A doubling in the degradation rate was also observed with a 10 °C increase in soil temperature. McGahey and Bouwer (1992) concluded that microorganisms naturally occurring in soils and groundwater are effective in biodegrading ethylene glycol with the half-life ranging from 0.2 to 0.9 days. Klecka et al. (1993) studied the biodegradation of aircraft de-icing fluids in soils adjacent to airport runways at various ethylene glycol concentrations and at various temperatures ranging from -2 to 25 °C. Generally, the rate of biodegradation of ethylene glycol was faster in soils with low glycol concentrations, high organic carbon content, and higher ambient soil temperatures (in the range of -2 to 25 °C). Ethylene glycol present in soils at concentrations <6,000 mg/kg (ppm) biodegraded at an average rate of 3.0 mg/kg (ppm) soil /day at -2 °C, at 19.7 mg/kg (ppm) soil/day at 8 °C, aud at an average rate of 66.3 mg/kg (ppm) soil/day at 25 °C (Klecka et al. 1993). Based on these results, biodegradation is expected to play a major role in removing ethylene glycol residues from soils adjacent to airport runways and taxiways.

As in surface waters, abiotic transformation of ethylene glycol in soil is not expected to be a significant process (EPA 1987a).

Biodegradation by a variety of microorganisms under both aerobic and anaerobic conditions is also the most important transformation process for propylene glycol in soils, with half-lives similar to or less than those in surface waters (EPA 1987a). The soil microbe C. glycolicum degraded propylene glycol under anaerobic conditions to acid and alcohol end products (Gaston and Stadtman 1963). Ouattara et al. (1992) reported anaerobic degradation of propylene glycol by strains of the sulfate-reducing bacteria Desulfovibrio isolated from anoxic soil of a rice field. Propylene glycol was degraded to acetate in the presence of sulfate with the production of carbon dioxide. The rates of biodegradation of propylene glycol in soils are significantly dependent on substrate concentrations, soil types, and ambient soil temperatures, but nutritional supplements had minimal effects (Klecka et al. 1993). Generally, the rate of propylene glycol biodegradation was faster in soils with low glycol concentrations, high organic carbon content, and higher ambient soil temperatures (in the range of -2-25 °C). Propylene glycol present in soils at concentrations <6,000 mg/kg (ppm) biodegraded at an average rate of 2.3 mg/kg soil/day at -2 °C, 27.0 mg/kg (ppm) soil/day at 8 °C and at an average rate of 93.3 mg/kg (ppm) soil/day at 25 °C (Klecka et al. 1993). Based on these results, biodegradation is expected to play a major role in removing propylene glycol residues from soils adjacent to airport runways and taxiways.

As in surface waters, abiotic transformation of propylene glycol in soil is not expected to be a significant process (EPA 1987a).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Ethylene glycol was detected in ambient air samples, at time-weighted average (TWA) concentrations of <0.05-0.33 mg/m^3 as aerosol and <0.05-10.4 mg/m3 as vapor, following spray application of de-icing fluids containing 50% solutions of the compound to the surfaces of bridges. The ambient air samples were collected above the sprayed bridges (LDOTD 1990).

No information was located on the concentration of propylene glycol in the ambient atmosphere. Propylene glycol was detected in air samples collected in a large scale environmental chamber analyzing volatile organic emissions. Quasi-steady-state emission rates of the propylene glycol at

24 hours and 168 hours after the start of the experiment were 690 μg/m^2/hour and 193 μg/m^2/hour, respectively from newly installed carpet with polyvinylchloride backing (Hodgson et al. 1993).

5.4.2 Water

Available information on the environmental impact of de-icing solutions on airport storm water runoff has been summarized in a recent review article by Sills and Blakeslee (1992). Monitoring data from several contractor and airport authority reports reveal that storm water runoff from airports may contain several hundred to several thousand mg/L (ppm) glycols. Ethylene glycol levels up to 19,000 mg/L (ppm) were detected in storm water from the Salt Lake City International Airport. The concentration of ethylene glycol in runoff from runway apron areas at the Toronto International Airport ranged from 75.0 mg/L to 3,100 mg/L (ppm) and was up to 70 mg/L (ppm) in a stream that received runoff from the airport. The concentration of ethylene glycol in storm water runoff from Stapleton International Airport in Denver, Colorado ranged from near zero to 5,050 mg/L (ppm). Although the potential for groundwater contamination is quite low for many airports with predominantly heavy soil, the movement of glycols through unsaturated silty sand can be potentially high (Sills and Blakeslee 1992). Thus, although ethylene glycol was not detected even in shallow soils at the edge of the runway at the Stapleton International Airport, the groundwater in the perched water table at Ottawa International Airport in Canada, which contained sandy soil, was found to contain ethylene glycol at levels up to 415 mg/L (ppm). Peak concentrations occurred in June and declined to nondetectable levels by the fall.

Available information on the environmental impact of de-icing solutions on airport storm water runoff has been summarized in a recent review article by Sills and Blakeslee (1992). Monitoring data from several contractor and airport authority reports reveal that storm water runoff from airports may contain several hundred to several thousand mg/L (ppm) glycols. Propylene glycol levels up to 19,000 mg/L (ppm) were detected in storm water from the Salt Lake City International airport. Although the potential for groundwater contamination is quite low for many airports with predominantly heavy soil, the movement of glycols through unsaturated silty sand can be potentially high (Sills and Blakeslee 1992). At the Ottawalntemational Airport in Canada, groundwater in the perched water table, which contained sandy soil, was found to contain propylene glycol at levels up to 4 mg/L (ppm). Peak concentrations occurred in June and declined to nondetectable levels by the fall.

5.4.3 Sediment and Soil

No information was found on soil concentrations of ethylene glycol or propylene glycol.

5.4.4 Other Environmental Media

Ethylene glycol has been identified in negligible amounts in the water-soluble component of cigarette smoke (Schumacher et al. 1977).

Ethylene glycol has been found to migrate into a number of foods from regenerated cellulose films containing triethylene glycol and polyethylene glycol as softening agents. Ethylene glycol was detected in fruit cakes at 27-34 mg/kg (ppm) after 84-336 days of storage, in meat pies at <10 mg/kg (ppm) after 3-7 days of storage, in toffee at <10-22 mgkg (ppm) after 168-450 days of storage, in madeira cake at <10-22 mg/kg (ppm) after 21-28 days storage, and in boiled sweets at 14-34 mg/kg (ppm) after 168-450 days storage (Castle et al. 1988a). Ethylene glycol also has been found to migrate into food simulants from polyethylene terephthalate (PET) bottles used in the packaging of carbonated beverages. The compound was detected at a concentration of about 100 ppb (0.1 ppm) in a 3% acetic acid solution used as a food simulant after 6 months of storage at 32 °C (Kashtock and Breder 1980). The source of ethylene glycol in this food simulant is the small amount of unreacted ethylene glycol in the polyethylene terephthalate polymer.

Propylene glycol have been identified in negligible amounts in the water-soluble component of cigarette smoke (Schumacher et al. 1977).

Propylene glycol has also been found to migrate into a number of foods from regenerated cellulose films containing the compound as a softening agent. The compound was detected in chocolates at 20-l ,460 mg/kg (ppm) after 5.5 months of storage and at 25-1,890 mg/kg (ppm) after 15 months, in fruit cakes at 10-154 mg/kg (ppm) after 84-336 days of storage, in meat pies at <10-118 mg/kg (ppm) after 3-7 days of storage, in toffee at <10-l,530 mg/kg (ppm) after 168-450 days of storage, in madeira cake at <10-365 mg/kg (ppm) after 21-28 days storage, and in boiled sweets at <10-272 mg/kg (ppm) after 168-450 days storage (Castle et al. 1988a).

Propylene glycol is also used in some cosmetic and oral drug formulations and is a GRAS additive in foods (FDA 1982), where it is used as an emulsifying and plasticizing agent, humectant, surfactant,

and solvent. Propylene glycol is added to foods at concentrations ranging from <0.001% in eggs and soups to up to 97% in seasonings and flavors (EPA 1979). Propylene glycol is a naturally occurring by-product in the fermentation of some beers and has been detected in the concentration range of 1.0-51.0 mg/L (ppm) in several commercially packaged beers (Williamson and Iverson 1993).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The most important route of human exposure to ethylene glycol for members of the general population is dermal contact with fluids used in automobiles (e.g., antifreeze, coolants, brake fluids). However, intentional or accidental ingestion of antifreeze by children and adults has caused the most morbidity and mortality in the past.

The National Occupational Exposure Survey (NOES) conducted by NIOSH during 1981-83 estimated 1.5 million workers are potentially exposed to ethylene glycol each year (NIOSH 1990). Contact with the skin and eyes is the most likely route of worker exposure to ethylene glycol. Inhalation may be an important route of human exposure under occupational conditions where the compound is heated or if mists are generated by heat or violent agitation (Rowe and Wolf 1982). Air samples taken from the breathing zones of workers applying de-icing fluids (50% ethylene glycol) to bridge surfaces contained the compound at concentrations of <0.0.5-2.33 mg/m^3 as aerosols and <0.05-3.37 mg/m^3 as vapors (LDOTD 1990).

The general population is exposed to propylene glycol primarily through ingestion of food and pharmaceutical products and through dermal contact with cosmetic products containing the compound (EPA 1979, 1987a). The average daily dietary intake of propylene glycol in Japan, where the compound is used as a food additive stabilizer, was estimated to be 43 mg per person in 1982 (Louekari et al. 1990). Public school children and the general public who participate in fire fighting exercises/demonstrations where propylene glycol is used to simulate fire conditions are exposed to small amounts of propylene glycol (Ross01 1993). The general public is exposed to low. concentrations of propylene glycol mist from propylene glycol-containing theatrical fog/smoke used in producing special effects during theatrical performances, rock concerts, and private parties (Ross01 1993). The general public is also exposed to small concentrations of propylene glycol from carpets with polyvinyl chloride backing. The quasi-steady-state specific emission rate of propylene glycol

from these carpets was calculated to be 690 μg/m^2/hour at 24 hours and 193 μg/m^2/hour at 168 hours after carpet installation (Hodgson et al. 1993).

NOSH estimated that about 2.5 million individuals were potentially exposed to propylene glycol in the workplace in 1970; the estimate for 1980 was 80,200 workers (HSDB 1995b). Dennal contact is expected to be the main route of worker exposure; however, inhalation of vapors or mists may also occur when the compound is heated, agitated, or sprayed (e.g., in de-icing formulations) (Rowe and Wolf 1982).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers in industries involved in the manufacture or use of products containing high concentrations of ethylene glycol (e.g., antifreeze, coolants, de-icing fluids, brakes fluids, solvents) may be exposed to concentrations of the compound at levels higher than the general population, particularly in operations involving heating or spraying of these materials.

Members of the general population who currently have potentially high exposures to ethylene glycol include individuals living near sites where ethylene glycol is manufactured or used, and individuals living near waste disposal sites contaminated with ethylene glycol. Persons living near airports where large amounts of ethylene glycol are used for de-icing of aircraft or near hazardous waste sites are potentially at greater risk of exposure, particularly from consumption of contaminated groundwater.

Workers in industries involved in the manufacture or use of products containing high concentrations of propylene glycol (e.g., antifreeze, coolants, de-icing fluids, brakes fluids, solvents) may be exposed to concentrations of the compounds at levels higher than the general population, particularly in operations involving heating or spraying of these materials. Performers and workers in theatrical productions that use propylene glycol-containing fog/smoke for special effects are likely to be exposed to higher concentrations of propylene glycol than the general population (Ross01 1993). Fire fighters who participate in frequent fire-fighting exercises involving propylene glycol fog/smoke may also belong to the high exposure group (Rosso1 1993).

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of ethylene glycol and propylene glycol is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of ethylene glycol and propylene glycol.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. As seen in Table 3-2, the relevant physical and chemical properties of ethylene glycol are known (Daubert and Danner 1989; HSDB 1995a; Merck 1989; Rowe and Wolf 1982; Weast 1988) and predicting the environmental fate and transport of ethylene glycol based on the K_{ow}, K_{oc}, and Herry's law constant is possible. No further information is required.

As seen in Table 3-2, the relevant physical and chemical properties of propylene glycol are known (ASTER 1995b; Dauber-t and Danner 1989; EPA 1987a; HSDB 1995b; Merck 1989) and predicting the environmental fate and transport of ethylene glycol based on the K_{ow}, K_{oc}, and Henry's law constant is possible. No further information is required.

Production, Import/Export, Use, Release, and Disposal. Knowledge of production and use data for a chemical is important in predicting its potential for environmental contamination and human exposure. Recent production data are available for ethylene glycol (SRI 1989, 1991, 1993). Similarly, data on the import/export volumes for ethylene glycol for the last several years are available (NTDB 1995). Information on the various uses of this compound are also available (Browning 1965; HSDB 1995a; Lewis 1993; Merck 1989; Rowe and Wolf 1982). Ethylene glycol enters the environment

primarily during its use as an ingredient in hydraulic brake fluids, as a component of automotive antifreeze/coolants, as a de-icing fluid for aircraft, and in its use as an intermediate in the synthesis of polyester fibers (Klecka et al. 1993; Lewis 1993; Merck 1989; Rowe and Wolf 1982). Major sources of ethylene glycol releases to soils are from the disposal of used antifreeze and de-icing solutions in hazardous waste sites (EPA 1979, 1987a; Ware 1988). Information regarding the disposal of ethylene glycol-containing waste waters (Rice et al. 1993; Wang et al. 1993) and for remediation of ethylene glycol contaminated soils (Drajun 1991; Vesper et al. 1994) is available.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1988-1993, became available in May of 1995. This database will be updated yearly and should provide a list of industrial facilities and emissions. TRI data are available for ethylene glycol because this chemical is required to be reported by chemical producers (EPA 1995c).

Recent production data are available for propylene glycol (SRI 1989, 1991, 1993, 1995). Similarly, data on the import/export volumes for propylene glycol for the last several years are available (NTDB 1995). Information on the various uses of this compound are also available (EPA 1987a; HSDB 1995b; Lewis 1993; Merck 1989; Rowe and Wolf 1982). Propylene glycol enters the environment primarily during its use as an intermediate in the synthesis of polyester fibers and resins, as a component of automotive antifreeze/coolants, and as a de-icing fluid for aircraft (Kirk-Othmer Encyclopedia of Chemical Technology 1978; Klecka et al. 1993; Lewis 1993; Merck 1989; Rowe and Wolf 1982). Propylene glycol is also used in pharmaceutical products, hair colorant formulations, food and tobacco products, as a non-toxic antifreeze in the food industry, as an air sterilant in hospitals or animal facilities, and as a special effects fog/smoke in theatrical performances or in fire training programs (Kirk-Othmer Encyclopedia of Chemical Technology 1978; Klecka et al. 1993; Merck 1989; Ross01 1993; Rowe and Wolf 1982). Information regarding the disposal of propylene glycolcontaining waste waters (Chou et al. 1979; Raja et al. 1991) and for remediation of propylene glycol contaminated soils (Drajun 1991; Vesper et al. 1994) is available.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1988-1993,

became available in May of 1995. This database will be updated yearly and should provide a list of industrial facilities and emissions. No TRI data are available for propylene glycol because this chemical is not required to be reported by chemical producers (EPA 1995c).

Environmental Fate. Information regarding the fate of ethylene glycol in the air is available that suggests the compound would be primarily found in the vapor phase and would likely be removed from the atmosphere via wet deposition (Eisenreich et al. 1981; EPA 1979). Ethylene glycol undergoes rapid photochemical oxidation via reaction with hydroxyl radicals with an estimated halflife of 8-84 hours (EPA 1987a; Howard et al. 1991). Because of its high solubility in water, the compound is expected to be transported primarily in aqueous media (EPA 1979) and will not partition to the atmosphere via volatilization from water (Thomas 1990). Adsorption to sediment or soil particles is not expected to be significant based on the low K_{oc} value; therefore, ethylene glycol is expected to have a high mobility in soil and potential to leach into groundwater (Swarm et al. 1983). Ethylene glycol is degraded in both water (Battersby and Wilson 1989; Bieszkiewicz et a1.1979; Caskey and Taber 1981; Child and Willetts 1978; Dwyer and Tiedje 1983; Evans and David 1974; Gonzalez et al. 1972; Watson and Jones 1977; Willetts 1981) and soil (EPA 1987a: Gaston and Stadtman 1963; LDOTD 1990; Klecka et al. 1993; McGahey and Bouwer 1992) primarily by biodegradation. Howard et al. (1991) estimated a half-life of 2-12 days for ethylene glycol in surface water under aerobic conditions and 8-48 days under anaerobic conditions, while the half-life of ethylene glycol in soil due to biodegradation was estimated to be 0.2-0.9 days. No additional information on degradation of ethylene glycol in air, water or soil are required.

Information regarding the fate of propylene glycol in the air is available that suggests the compound would be primarily found in the vapor phase and would likely be removed from the atmosphere via wet deposition (Eisenreich et al. 1981; EPA 1979, 1987a). Propylene glycol undergoes rapid photochemical oxidation via reaction with hydroxyl radicals with an estimated half-life of 20 hours in the atmosphere (EPA 1987a). Because of its high solubility in water, the compound is expected to be transported primarily in aqueous media and will not partition to the atmosphere via volatilization from water (EPA 1979, 1987a; Thomas 1990). Adsorption to sediment or soil particles is not expected to be significant based on the low K,, value and therefore propylene glycol is expected to have a high mobility in soil and potential to leach into groundwater (Swarm et al. 1983). Propylene glycol is transformed in both water and soil by microorganisms (EPA 1987a; Gaston and Stadtman 1963; Klecka et al. 1993). The half-lives for the biotransformation of propylene glycol in surface waters

generally range from 1 to 4 days under aerobic conditions and from 3 to 5 days under anaerobic conditions, with half-lives in soil similar to or less than those in surface waters (EPA 1987a). No additional information on degradation of propylene glycol in air or water are required; however, additional quantitative information on the degradation of propylene glycol in soil would be useful.

Bioavailability from Environmental Media. Available information regarding the rate of ethylene glycol absorption following inhalation, oral, or dermal contact has been discussed in the Toxicokinetics section (see Section 2.3). Although no data on ethylene glycol's bioavailability from contaminated air are available, the bioavailability from inhalation exposure is expected to be high because ethylene glycol is likely to be present in the vapor phase (Eisenreich et al. 1981) and not in the particulate phase in the adsorbed state. Similarly, no data on the bioavailability of ethylene glycol from water, soil or plant material are available; however, ethylene glycol is readily miscible in water and does not adsorb readily to soil. Ethylene glycol, therefore, is expected to be readily bioavailable from soil and water. Information on the bioavailability of ethylene glycol from actual environmental media needs further development.

Reliable monitoring data for the levels of ethylene glycol in contaminated media at hazardous waste sites are needed so that the information obtained on levels of ethylene glycol in the environment can be used in combination with the known body burdens of ethylene glycol to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Available information regarding the rate of propylene glycol absorption following inhalation, oral, or dermal contact has been discussed in the Toxicokinetics section (see Section 2.3). Although no data on propylene glycol's bioavailability from contaminated air are available, the bioavailability from inhalation exposure is expected to be high because propylene glycol is likely to be present in the vapor phase (Eisenreich et al. 1981) and not in the particulate phase in the adsorbed state. Similarly, no data on the bioavailability of propylene glycol from water, soil or plant material are available; however, propylene glycol is readily miscible in water and does not adsorb readily to soil.. Propylene glycol, therefore, is expected to be readily bioavailable from soil and water. Information on the bioavailability of propylene glycol from actual environmental media is not required as propylene glycol is a GRAS chemical (FDA 1982).

Because the FDA (1982) has classified propylene glycol as a GRAS chemical, no monitoring data for concentrations of propylene glycol in contaminated media at hazardous waste sites are needed to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Food Chain Bioaccumulation. Based on its low K_{oc}, value, ethylene glycol is not expected to bioconcentrate in aquatic food chains. In laboratory exposure studies, ethylene glycol does not bioconcentrate to any great extent in fish, crayfish, or algae (Freitag et al.1985; Khoury et al. 1993); however, measured BCF values are not available for a large number of edible invertebrate and fish species. Information is also lacking regarding the biomagnification potential of ethylene glycol through aquatic food chains although biomagnification is probably a minor process because of the rapid degradation rate for the chemical in aquatic systems. No further information on the bioconcentration or biomagnification potential of ethylene glycol are required.

Based on its low K_{oc} value, propylene glycol is not expected to bioconcentrate in aquatic food chains; however, no measured BCF values were located for any invertebrate or fish species. Information is also lacking regarding the biomagnification potential of propylene through aquatic food chains although it is unlikely because of the rapid degradation rate for the chemical in aquatic systems. No further information on the bioconcentration or biomagnification potential of propylene glycol is required as it is a GRAS chemical (FDA 1982).

Exposure Levels in Environmental Media. Little quantitative information was located on the concentration of ethylene glycol in ambient air. TWA concentrations of the compound as both an aerosol and a vapor were measured following the spray application of de-icing fluids containing ethylene glycol on a bridge (LDOTD 1990). These data are not general enough to estimate inhalation exposure to ethylene glycol for the general population in the United States. Ethylene glycol was detected in air samples collected at four hazardous waste sites (HazDat 1995). No data on the level of ethylene glycol in drinking water were located, although ethylene glycol has been detected at up to 415 mg/L (ppm) in groundwater in the vicinity of an airport (Sills and Blakeslee 1992) and in groundwater samples collected at 7 hazardous waste sites (HazDat 1995). Little information on the levels of ethylene glycol in soils was located. Ethylene glycol was detected in a soil sample collected (at an unspecified depth) at one hazardous waste site (HazDat 1995). Additional information regarding the levels of ethylene glycol in ambient air, in drinking water, and in soil is needed. Some data on

ethylene glycol levels in foods, particularly those stored in cellulose films or in PET bottles are available (Castle et al. 1988a; Kashtock and Breder 1980). Additional quantitative information on current levels of ethylene glycol in various environmental media and levels of contamination in foods would be helpful in assessing the health risks to the general population and in occupational settings.

Reliable monitoring data for the levels of ethylene glycol in contaminated media at hazardous waste sites are needed so that the information obtained on levels of this compound in the environment can be used in combination with the known body burden of ethylene glycol to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

No information was located on the concentration of propylene glycol in ambient air. Propylene glycol was detected in air samples collected in a large scale environmental chamber analyzing volatile organic emissions from newly installed carpet with polyvinylchloride backing (Hodgson et al. 1993). No data on the level of propylene glycol in drinking water were located, although propylene glycol has been detected at up to 4 mg/L (ppm) in groundwater in the vicinity of an airport (Sills and Blakeslee 1992) and at unspecified concentrations in groundwater samples collected at two hazardous waste sites (HazDat 1995). Little information on the levels of propylene glycol in soils was located. Data on propylene glycol levels in foods, particularly those stored in cellulose films or in PET bottles, are available (Castle et al. 1988a; EPA 1979; Kashtock and Breder 1980; Williamson and Iverson 1993) and a recent estimate of human dietary intake of propylene glycol in Japan is available (Louekari et al. 1990). Reliable monitoring data for the levels of propylene glycol in various environmental media are not needed as this compound is a GRAS additive in foods (FDA 1982).

Exposure Levels in Humans. Little quantitative information on ethylene glycol levels in various human tissues and body fluids of a control population, populations near hazardous waste sites, or occupationally exposed groups in the United States is available. Most information is available for oral exposures derived from intentional or accidental poisonings (Gabow et al. 1986; Hewlett et al. 1986; Jacobsen et al. 1988; Parry and Wallach 1974; Robinson and McCoy 1989; Vale 1979; Wiener and Richardson 1988). Some information is available on plasma glycolate levels for poisoning victims admitted to a hospital (Jacobsen et al. (1984), and on urine and other tissues (Cheng et al. 1987; Rothman et al. 1986; Winek et al. 1978). Data are needed on the levels of ethylene glycol and its metabolites in body tissues and fluids especially from dermal and inhalation studies. Information on control populations, populations that live in the vicinity of hazardous waste sites, and those who are

occupationally exposed to ethylene glycol is needed. This information is necessary for assessing the need to conduct health studies on these populations.

Little quantitative information on propylene glycol levels in various human tissues and body fluids of a control population, populations near hazardous waste sites, or occupationally exposed groups in the United States is available. Most information is available for oral exposures (Yu et al. 1985). Data on the levels of propylene glycol and its metabolites in body tissues and fluids are not needed because this chemical is a GRAS food additive (FDA 1982).

Exposure Registries. No exposure registries for ethylene glycol were located. This substance is not .currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

No exposure registries for propylene glycol were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

5.7.2 Ongoing Studies

No additional information was located on ongoing studies that would fill existing data needs for ethylene glycol or propylene glycol (FEDRIP 1995).

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring ethylene glycol or propylene glycol in biological samples or in environmental media. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify ethylene glycol or propylene glycol. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect ethylene glycol or propylene glycol in environmental samples are the methods approved by federal organizations such as EPA and the National Institute for Occupational Safety and Health (NTOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL SAMPLES

Table 6-l is a summary of some of the most commonly used methods reported in the literature for detecting propylene glycol and ethylene glycol in biological samples. The primary method for measuring ethylene glycol or propylene glycol in biological samples is derivatization followed by gas chromatography (GC) using either a flame ionization detector (FID) or mass spectrometry (MS) for quantification. GC is the preferred analytical method because of the ease of sample preparation and the accuracy of the quantification of sample concentrations. Alkali flame ionization detectors have also been used for ethylene glycol analysis and give a response ratio of 3:l compared with PID (Bogusz et al. 1986). Capillary gas chromatography with a constant current ^{63}Ni electron capture detector (ECD) has also been used successfully to detect propylene glycol (Needham et al. 1982).

Sample preparation for GC is important and proceeds through several steps: acidification, esterification, and extraction into an organic solvent. The use of internal standards is necessary for quantification. In clinical cases involving ethylene glycol poisoning, propylene glycol should not be used as an internal standard for quantitation because certain sedatives (Valium and Ativan) may contain propylene glycol (Apple et al. 1993).

Table 6-1. Analytical Methods for Determining Ethylene Glycol and Propylene Glycol in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human plasma (EG and PG)	Deproteinization with acetic acid; vortex; centrifugation; supernatant spiked with internal standard; reaction with butylboronic acid; neutralize with NH_4OH, extraction with dichloromethane; concentration.	HRGC/MS	5 ppm (EG); 1 ppm (PG)	94–106	Giachetti et al. 1989
Human serum (PG)	Acetonitrile with internal standard added to sample; centrifugation; concentration; extraction with *p*-bromophenyl boric acid in ethyl acetate.	HRGC/ECD	0.38 ppm	>90	Needham et al. 1982
Human serum (EG)	Internal standard (in acetonitrile) added to sample; centrifugation to remove protein precipitate; esterification with butylboronic acid and 2,2-dimethoxypropane; neutralization with NH_4OH in acetonitrile.	HRGC/FID	NR	95	Smith 1984
Human blood (PG)	Deproteinization with $HClO_4$; centrifugation; pH adjustment; centrifugation.	GC/MS	0.6 ppm	NR	Sisfontes et al. 1986
Human serum and urine (EG, PG)	Internal standard added; centrifugation; derivatization with phenylboronate in methanol.	HRGC/FID	1.0 ppm	89–98	Houźe et al. 1993
Human blood/ tissue (EG)	Anhydrous Na_2SO_4 ground with sample; derivatization with *n*-butylboronic acid in acetone containing internal standard; centrifugation or filtration.	GC/FID/AFID	NR	70	Bogusz et al. 1986

Table 6-1. Analytical Methods for Determining Ethylene Glycol and Propylene Glycol in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human serum (glycolic acid)	Colorimetric: precipitation of protein with trichloroacetic acid followed by centrifugation, addition of chromotropic acid, heating, and dilution. Gas chromatographic: addition of internal standard and acetone followed by centrifugation, addition of NaOH, evaporation to dryness, and formation of methyl ester.	Absorbance at 580 nm or GC/FID as appropriate	1.0 mmol/L (60 ppm, w/v) for both methods; 3–6% RSD	NR	Fraser and MacNeil 1993
Humans serum (glycolic acid)	Extraction from salted, acidified serum using methyl ethyl ketone followed by removal of organic phase and evaporation to dryness and derivatization with PNBDI.	HPLC/UV	0.05 mmol/L (3 ppm, w/v); 1% RSD	NR	Hewlett et al. 1986
Urine (EG)	Acidification; extraction with $CHCl_3$; concentration; TLC.	TLC	NR	NR	Riley et al. 1982
Urine (sodium fluorescein) (EG)	Untreated samples read in borosilicate tubes.	Fluorescence (Wood's lamps)	NR	NR	Winter et al. 1990
Dog urine (glycolic acid) (EG)	Dilution; NaCl addition and acidification; extraction in MEK; evaporation; dissolution of residue in ethylacetate; derivatization with PNBDI.	HPLC/UV	1–2 ng	96	Hewlett et al. 1983
Human plasma, urine (oxalate)	Heparinized blood deproteinated by addition of acetonitrile and phosphate buffer (pH = 7), centrifugation, removal of solvent and evaporation to dryness; derivatization as for urine; Urine acidified and derivatized using 1,2-diaminobenzene, adjustment of pH to 5–6, centrifugation.	HPLC/UV	Plasma: 0.15 mg/L (ppm, w/v); 7.5% RSD. Urine: 0.5 mg/L (ppm, w/v); 5% RSD.	85	Brega et al. 1992

Table 6-1. Analytical Methods for Determining Ethylene Glycol and Propylene Glycol in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Kidney tissue dog (hippurate) (EG)	Tissue ground with acidic methanol; filtration; concentration; spot on 254 nm TLC plate.	TLC	NR	NR	Riley et al. 1982
Human tissue (EG)	Samples extraction in HPLC grade water for 24 hours; filtration of supernatant.	HPLC/RI	5 ppm	98 at 1 mg/mL (1000 ppm)	Wu and Malinin 1987

AFID = alkali flame ionization detector; ATP = adenosine triphosphate; $CHCl_3$ = chloroform; CH_3OH = methanol; ECD = electron capture detector; EG = ethylene glycol; FID = flame ionization detector; GC = gas chromatography; HCl = hydrochloric acid; $HClO_4$ = chloroform; HPLC = high-performance liquid chromatography; HRGC = high resolution gas chromatography; KOH = potassium hydroxide; MEK = methyl-ethyl ketone; $MgSO_4$ = magnesium sulfate; MS = mass spectrometry; NaCl = sodium chloride; NAD = nicotinamide adenine dinucleotide; Na_2SO_4 = sodium sulfate; NH_4OH = ammonium hydroxide; NR = not reported; PG = propylene glycol; PNBDI = O-*p*-nitrobenzyl-N,N'-diisopropylisourea; RSD = relative standard deviation; RI = refractive index detector; TLC = thin-layer chromatography; UV = ultraviolet detector w/v = weight:volume

6. ANALYTICAL METHODS

Detection of propylene glycol and ethylene glycol in biological samples using GC with either FID or MS is very sensitive, with detection limits ranging from sub to low ppm. The coefficient of variation (CV) varies with the concentration of glycol used but typically ranges from 0.4% to 27% and is usually less than 10%. In gas chromatographic procedures, the glycols and their acid metabolites are derivatized to form esters in order to facilitate quantitative elution from the chromatographic columns (see Table 6-l). Simple and rapid methods are also available for the quantitation of the glycols in urine, serum, or deproteinated whole blood. These methods use direct sample injection without prior solvent extraction and derivatization (Aarstad et al. 1993; Edinboro et al. 1993; Jonsson et al. 1989). However, such methods, particularly those that use packed columns may misidentify propionic acid (found in patients with methylmalonic acidemia) as ethylene glycol (Shoemaker et al. 1992).

High performance liquid chromatography (HPLC) has also been used to identify ethylene glycol and its metabolites such as glycolate (Hewlett et al. 1983, 1986), hippurate (Riley et al. 1982), and oxalate (Brega et al. 1992) in biological samples, particularly blood and urine. Positive results may be confirmed with GC/MS. This makes GC/MS the preferred method since the HPLC step can be omitted. However, HPLC methods to measure plasma levels of glycolate have been used to aid in diagnosis and treatment of ethylene glycol poisoning (Hewlett et al. 1986; Jacobsen et al. 1988). Gas chromatographic and calorimetric methods for quantification of glycolate have been presented (Fraser and MacNeil 1993).

High-resolution proton nuclear magnetic resonance spectroscopy has potential use in the identification and quantification of propylene glycol and other chemicals in cerebrospinal fluid (CSF) and serum (Petroff et al. 1986). The technique has two advantages: 1) it requires no pretreatment of the specimens prior to analysis and no advance knowledge of possible compounds present in fluids and 2) results are extremely rapid. Propylene glycol was detected at 1 ppm in CSF (Petroff et al. 1986).

Microscopy can be used to identify metabolic products of ethylene glycol. Scanning electron microscopy (SEM) at 20 kilovolts will detect crystals of calcite, calcium oxalate monohydrate, and calcium oxalate dihydrate in kidney tissue (Siew et al. 1975b). Phase-contrast polarization and light microscopy X-ray powder diffraction may be used to identify hippuric acid crystals in urine (Foit et al. 1985).

6. ANALYTICAL METHODS

The use of ethylene oxide to sterilize tissue for transplantation may result in the formation of ethylene glycol when ethylene oxide is in prolonged contact with tissue. To quantify the formation of ethylene glycol in tissue, an HPLC method using a differential refractive index detector has been developed. The HPLC system can be used to detect ppm levels of ethylene glycol with a sensitivity of $2x10^{-6}$ refractive index unit full scale. This procedure has three advantages: 1) requires only 4 minutes for analysis, 2) simple sample preparation, and 3) good reproducibility (Wu and Malinin 1987).

Techniques using gas chromatography and various detection systems to detect and quantify ethylene glycol in human blood have been developed for use in hospital laboratories to assist in the diagnosis of ethylene glycol poisoning (caused by drinking antifreeze containing ethylene glycol). These techniques are quite rapid, usually less than 30 minutes, and do not require elaborate sample preparation. Some may also be used for detection of propylene glycol. The specific techniques used for each analytical method are listed in the table if that information was provided by the author(s).

An alternative method, developed in a hospital, for detecting ethylene glycol in blood is the use of the DuPont *Automated Clinical Analyzer* triglyceride assay pack. This enzymatic method, while relatively simple, cannot be used when the triglyceride concentration of the serum exceeds 12 g/L and requires that positive results for ethylene glycol be confirmed using another method (Ochs et al. 1988; Ryder et al. 1986). The enzymatic method has been modified to eliminate some of the interference problems present in the earlier methods (Blandford and Desjardins 1994).

Thin-layer chromatography (TLC) with a chloroform solvent has been used to detect ethylene glycol and its metabolites in urine or renal tissue (Riley et al. 1982). Metabolites of ethylene glycol in the blood may be detected by analytical isotachophoresis using a system equipped with both a conductivity detector and an ultraviolet detector. Blood and serum samples should not have been previously treated with oxalate, citrate, or ethylene diamine tetracetic acid. This technique may be of value when ethylene glycol poisoning is suspected but sufficient time has elapsed for metabolism of the compound to have occurred (Ovrebo et al. 1987). A simple and rapid calorimetric method that uses chromatropic acid has been proposed for the quantitation of glycolic acid, the major toxic metabolite of ethylene glycol (Fraser and MacNeil 1993).

No information was located on detecting ethylene glycol or propylene glycol in feces, adipose tissue, or human milk.

6.2 ENVIRONMENTAL SAMPLES

As with biological samples, GC is the major technique used to determine ethylene or propylene glycol concentrations in environmental samples whether in air, water, food, drugs, or other substances. Capillary gas chromatography with FTD or ECD, possibly followed by MS, generally gives good quantitative results down to the ppm range with recovery usually greater than 80%. The determination of ethylene glycol or propylene glycol in air requires adsorption onto a surface and subsequent extraction. Water samples may be analyzed without preparation (EPA 1995a, 1995b). Detection of ethylene glycol or propylene glycol in foods and drugs may be accomplished by chromatography of the sample; for substances with a high fat content, extraction with hexane may be used to remove the fat. Table 6-2 is a summary of some of the most commonly used methods reported in the literature for detecting ethylene glycol or propylene glycol in environmental samples. The specific techniques used for each analytical method are listed in the table if that information was provided by the author(s).

Air sampling for ethylene glycol is performed by adsorption onto a resin column such as Amberlite XAD-2. Although activated charcoal filters have some utility, recovery is greater with the Amberlite, and it is the preferred adsorption medium. Ethylene glycol is then solvent-extracted with recovery of 98%. If activated charcoal is used for adsorption, 5% methanol in dichloromethane is the best solvent with maximum recovery of 84% (Andersson et al. 1982, 1984). An alternative method for sampling ethylene’glycol involves passage of air through a glass fiber filter with a silica gel tube. Ethylene glycol is then extracted in a 2-propanol:water solvent mixture and injected into the gas chromatograph (Tucker and Deye 1981). A slightly modified version of this method is the NIOSH-approved method for the determination of ethylene glycol in occupational air (see Table 6-2). The sensitivity of this method can be increased by use of a hot on-column injection technique using methanol as the solvent (Lang 1986).

A portable, automated, photoionization gas chromatograph has been used to detect ethylene glycol in air samples in industrial facilities at levels as low as 0.05 ppm (Adams and Collins 1988).

Ethylene glycol may be detected by a calorimetric reaction with 3-methyl-2-benzothiazolinone hydrazone hydrochloride after oxidation of the glycols to the corresponding aldehydes with acidified permanganate. The solution is read at 630 nm in a spectrophotometer. This method may be used for

Table 6-2. Analytical Methods for Determining Ethylene Glycol and Propylene Glycol in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air[a]	Sample collection on glass fiber filters and silica gel; extraction with 2-propanol:water.	GC/FID	2 ppm	81–111	NIOSH 1984
Air	Sample adsorbed on Amberlite® XAD-2 with personal sampling pump; extraction with diethyl ether.	GC/FID	NR	75–98	Anderson et al. 1982
Water	Direct injection (Method 8015b)	GC/FID	NR	NR	EPA 1995a
Water	Direct injection (Method 8430)	GC/FTIR	120 mg/L (ppm, w/v)	NR	EPA 1995b
Plastics	Sample extraction from plastic with carbon disulfide	GC/FID	16.5 ng	58–61	Muzeni 1985
Plastics	Sample extraction with solvent of ethylacetate-water-methanol	GC/FID	2 ppm	NR	DeRudder et al. 1986
Cosmetics (PG)	Co-distillation with isooctane.	GC/FID	NR	NR	Helrich 1990a
Ground tobacco	Extraction with anhydrous methanol.	GC/FID	NR	NR	Helrich 1990b
Aqueous solution	Sample concentration, then dilution with water; concentration with helium gas; redilution.	GC/FID	50 ppb	97–103	Kashtock and Breder 1980
Beer	Addition of ammonium sulfate and extract with ethyl acetate.	HRGC/FID	0.73 ppm	88	Williamson and Iverson 1993
Vanilla extract (PG)	Refluxing with heptane and addition of KIO_4, $NaHCO_3$, KI, and starch to aqeous phase followed by titration with $KasO_2$.	Titration	NR	NR	Helrich 1990c

TABLE 6-2. Analytical Methods for Determining Ethylene Glycol and Propylene Glycol in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Food	Addition of hot water to sample to obtain slurry; extraction with hexane; precipitation of sugars with calcium hydroxide; concentration; derivatization with BSTFA.	HRGC/FID GC/MS	10 ppm	78–107	Castle et al. 1988b
Anchovies	Extraction with methanol and concentration.	HRGC/MS/MS (PICI)	12.5 ppb	NR	Matusik et al. 1993

[a]For ethylene glycol only

BSTFA = bis(trimethylsilyl)trifluoroacetamide; FID = flame ionization; GC = gas chromatography; HRGC = high resolution gas chromatography; MS = mass spectrometry; MS/MS = tandem mass spectrometry; PG = propylene glycol; PICI = positive ion chemical ionization

ethylene glycol in water (Evans and Dennis 1973) or to detect ethylene oxide in air (Kring et al. 1984); however, this method is not quantitative and is relatively insensitive compared with GCMS.

The migration of ethylene glycol from plastics into solution can be studied with GC. Sample preparation methods include extraction in hydrochloric acid (Ball 1984) distilled water (Spitz and Weinberger 1971), carbon disulfide (Muzeni 1985), dimethylformamide (Danielson et al. 1990), and a mixture of ethyl acetate, water, and methanol (DeRudder et al. 1986). Other methods for detecting ethylene glycol in industrial products include HPLC (Aboul-Enein and Islam 1989) and a periodate flow-through ion-selective electrode (Diamandis et al. 1980).

The presence of ethylene glycol or propylene glycol in foods packaged with plastic films containing the compounds has been studied, as have ethylene glycol levels in drugs sterilized with ethylene oxide. Sample preparation is important because procedures vary depending on the fat content of the food sample. Foods with low fat content can be extracted with ethyl acetate, derivatized to a trimethylsilyl ether, and then injected into the gas chromatograph. For foods with a high fat content, hexane is used as the defatting agent prior to derivatization. Quantifying ethylene glycol or propylene glycol in wines requires no preparation of the samples prior to analysis (Kaiser and Rieder 1987; Klaus and Fischer 1987). Drugs in aqueous solutions may be analyzed directly, water insoluble drugs should be extracted in water, and ointments may be dissolved in hexane and then extracted with water. Recovery is between 80 and 114%, with detection limits in the low-ppm range (Hartman and Bowman 1977; Manius 1979). The use of ion exchange chromatography with sulfuric acid as the mobile phase has also given good recovery (98-101%) with a detection limit of 5 μg/rnL propylene glycol from pharmaceuticals (Iwinski and Jenke 1987). Although the use of TLC (Ballarin 1980) has been recommended, it has been superseded by GC.

Propylene glycol in cigarette smoke has been detected using electrostatic precipitation or filter pad, with extraction and separation with capillary gas chromatography (Borgerding et al. 1990).

No information was located on techniques for detecting and analyzing ethylene glycol and propylene glycol in soil.

6.3 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of ethylene glycol and propylene glycol is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of ethylene glycol and propylene glycol.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Methods are available for the determination of ethylene glycol in blood, tissue, and urine (Bogusz et al. 1986; Giachetti et al. 1989; Houze et al. 1993; Riley et al. 1982; Smith 1984; Wu and Malinin 1987) with sensitivities in the low and sub-ppm range. Methods for the determination of propylene glycol in blood and urine are also available (Giachetti et al. 1989; Houze et al. 1993; Needham et al. 1982; Sifontes et al. 1986) with sensitivities in the sub-ppm range. Methods are also available for metabolites of ethylene glyciol (glycolic acid, oxalic acid) in blood and urine (Brega et al. 1992; Fraser and MacNeil 1993; Hewlett et al. 1986) with sensitivities as low as 3 ppm for glycolic acid and of 0.15 ppm for oxalic acid. Glycolic .acid was identified in Chapter 2 as a sensitive biomarker of exposure to ethylene glycol. These methods seem to be adequate for the measurement of propylene glycol and ethylene glycol and its metabolites in the human population.

Serum concentrations of blood urea nitrogen (BUN) or creatinine can serve as indicators of renal toxicity (biomarkers of effect) induced by exposure to ethylene glycol but these are not specific for ethylene glycol intoxication (Grauer et al. 1987).

6. ANALYTICAL METHODS

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for the determination of ethylene glycol and propylene glycol have been reported for air (Anderson et al. 1982; NIOSH 1984), water or aqueous solutions (EPA 1995a, 1995b; Kashtock and Breder 1980), and foods (Castle et al. 1988b; Matusik et al. 1993; Williamson and Iverson 1993). Methods have also been developed for the determination of glycols that leach from plastics (DeRudder et al. 1986; Muzeni 1985) and that can end up m foods stored in containers made from the plastics.

The MRL for inhalation exposure to ethylene glycol is 0.5 ppm and thus requires a method .level of detection (LOD) of 0.5 ppm. This value is below the LODs of the methods reported. Although it should be possible to increase the sampling volumes and increase the sensitivities of the methods, this would need to be shown to be free of problems. Oral MRLs have been established to be 2 mg/kg/day for acute exposure and 0.2 mg/kg/day for chronic exposure. Assuming a 70-kg individual and oral intakes of either 2 L/day of water or 2 kg/day of food, analytical methods would need sensitivities below 70 ppm in water or food. The methods reported for aqueous solutions (LOD = 50 ppb, Kashtok and Breder 1980), beer (LOD = 0.73 ppm, Williamson and Iverson 1993), and foods (LOD= 10 ppm, Castle et al. 1988b; LOD =12.5 ppb, Matusik et al. 1993) should be adequate to measure acute exposure. However, chronic exposure requires method LODs of approximately 7 ppm and only the methods of Kashtock and Breder (1980) for aqueous solutions, Williamson and Iverson (1993) for beer, and Matsulik et al. (1993) for anchovies can meet this requirement. The applicability of these methods to other beverages and foods has not been demonstrated. Thus, additional methods should be developed and validated for ethylene glycol in other beverages and foods at concentrations relevant to the chronic oral MRL.

An MRL of 0.009 ppm for intermediate inhalation exposure to propylene glycol has been defined and none of the methods reported would be adequate without modification. It is likely that the LODs of some of the methods could be reduced but this remains to be shown.

6.3.2 Ongoing Studies

No ongoing research on analytical methods for the determination of ethylene or propylene glycol was found.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding ethylene glycol and propylene glycol in air, water, and other media are summarized in Tables 7-l and 7-2.

An MRL of 0.5 ppm has been derived for acute-duration inhalation exposure (14 days or less) to ethylene glycol, based on a NOAEL of 197 ppm for increased renal weight (Tyl 1988a).

An MRL of 2.0 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to ethylene glycol, based on a NOAEL of 150 mg/kg/day for developmental toxicity (skeletal alterations) (Tyl 1989).

An MRL of 2.0 mg/kg/day has been derived for chronic-duration exposure (365 days or more) to ethylene glycol, based on a NOAEL of 200 mgkg/day for the renal toxicity in rats (DePass et al. 1986a; Woodside 1982).

An MRL of 0.009 ppm has been derived for intermediate-duration inhalation exposure (1.5-364 days) to propylene glycol based on a LOAEL of 51 ppm for nasal hemorrhaging (Suber et al. 1989).

EPA (IRIS 1994) assigned ethylene glycol a reference dose (RfD) of 2.0 mg/kg/day with an uncertainty factor of 100 based on kidney toxicity in rats (DePass et al. 1986).

Ethylene glycol is on the list of chemicals appearing in “Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986” (EPA 1987b, 1987c). Comprehensive Environmental Response Compensation and Liability Act (CERCLA or Superfund) regulations require that accidental releases greater than 5,000 pounds of ethylene glycol be reported (EPA 1993a).

Both ethylene glycol and propylene glycol are regulated under Clean Air Act New Source Performance Standards for the synthetic organic chemical manufacturing industry (EPA 1993b).

Propylene glycol and ethylene glycol are regulated by the Clean Water Act Effluent Guidelines for organic chemicals, plastics, and synthetic fibers (OCPSF). The waste water generated by the

production of these chemicals has effluent limitations on biochemical oxygen demand (BOD_5), total suspended solids (TSS), and pH (EPA 1987d).

Table 7-1. Regulations and Guidelines Applicable to Ethylene Glycol

Agency	Description	Information	References
NATIONAL			
Regulations:			
a. Air:			
OSHA	Meets Criteria for Medical Records	Yes	29 CFR 1910.20 OSHA 1987 OSHA 1988
EPA	Hazardous Air Pollutants	Yes	U.S. Congress 1990
EPA OAR	App. A - Chemicals Defining Synthetic Organic Chemical and Polymer Manufacturing	Yes	40 CFR 52 EPA 1972a
	Subpart VV - Std. of Performance for Equipment Leaks of VOC in SOCMI: Chemicals Produced by Affected Facilities	Yes	40 CFR 60.489 EPA 1983
	Definitions of Emissions from Polymer Manufacturers: Definition of "Polymerization Reaction Section"	Yes	40 CFR 60.561 EPA 1990b
	Subpart NNN - Std. of Performance for VOC Emissions from SOCMI Distillation Operations: Chemical Affected	Yes	40 CFR 60.667 EPA 1990b
	Subpart RRR - Std. of Performance for VOC Emissions from SOCMI Process Reactors: Chemicals Affected	Yes	40 CFR 60.707 EPA 1993b
b. Water			
EPA OW	Commodity Organic Chemical Subcategory	Yes	40 CFR 414.60 EPA 1987d
c. Food:			
FDA	Indirect Food Additive for Use only As a Component of Adhesives.	Yes	21 CFR 175.105 FDA 1977a FDA 1977b
	2,4-D: Food Tolerances for Residues 2,4-D Applied in the Form of Polyethylene Glycol and/or Propylene Glycol Max. 2,4-D tolerance: Pasture and Rangeland Grasses Min. 2,4-D tolerance: Blueberries and Rice	 1000 ppm 0.1 ppm	40 CFR 180.142 EPA 1982
d. Other:			
EPA OERR	Toxic Chemical Release: Community Right to Know	Yes	40 CFR 372.65 EPA 1987b EPA 1987c
EPA	Reportable Quantity	5,000 lbs.	58 FR 54836 EPA 1993a

Table 7-1. Regulations and Guidelines Applicable to Ethylene Glycol (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
EPA OPTS	Premanufacture Notification Exemptions: Polymers - List of Reactants From Which Polyesters May be Made	Yes	40 CFR 723.250 EPA 1984b
Guidelines:			
a. Air:			
ACGIH	Ceiling Limit	127 mg/m^3 (50 ppm)	ACGIH 1994
EPA	Drinking Water Quality Guidelines	7,000 µg/L	FSTRAC 1990
NRC/NAS	Emergency Exposure Guidance Level	40 ppm (1 hour) 20 ppm (24 hours)	NRC 1994
b. Other:			
	RfD (oral) Carcinogenic Classification Unit risk (air) Unit risk (water)	2.0 mg/kg/day No data No data No data	IRIS 1994
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable ambient air concentrations		
	8 hours		
FL-Pinellas	24 hours	1.27x10^{-3} µg/m^3	Florida 1994
	8 hours	3.048x10^2 µg/m^3	
LA	24 hours	3.02x10^3 µg/m^3	NATICH 1991
MA	Annual	3.45x10^1 µg/m^3	
	1 hour	3.45x10^1	
ND	8 hours	1.27 mg/m^3	
NV	24 hours	2.98 mg/m^3	
OK	24 hours	1.27x10^4 µg/m^3	
VA	24 hours	1.1x10^3 µg/m^3	
WA-SWEST		4.16x10^2 µg/m^3	
STATE (cont.)			
KY	Significant Emission Levels of Toxic Air Pollutants	2.240x10^{-2} lbs/hour	401 KAR 63.022 NREPC 1986
	Effects Screening Level		
TX	30 minutes	260 µg/m^3	Texas 1994
	Annual	26 µg/m^3	
b. Water:			
	Drinking Water Quality Guidelines and Standards		FSTRAC 1990
AZ		5,500 µg/L	
CT		100 µg/L	
ME		5,500 µg/L	
MA		5,500 µg/L	
MN		14,000 µg/L	
NH		7,000 µg/L	
NJ		290 µg/L (future)	

Table 7-1. Regulations and Guidelines Applicable to Ethylene Glycol (continued)

Agency	Description	Information	References
STATE (Cont.)			
RI		7,000 µg/L	
VT		7 µg/L (standard)	
	Water Quality: Human Health		CELDs 1994
CO	Domestic water supply-gw	7,000 µg/L	
CT	Drinking water supply-action level	100 µg/L	
ME	Drinking water standards - misc. organic chemicals screening level number 2 - To be analyzed at state discretion, depending on results of screening level 1	Yes	
NH	Drinking water quality standards (MCLs)	Yes	
	SNARLS Toxic contaminant levels:		
	Length of exposure (1 day)	19 mg/L	
	Length of exposure (lifetime)	5.5 mg/L	
	Water Quality: Aquatic Life		CELDs 1994
OH	Criteria for Aquatic Life Habitat Use:		
	Coldwater, outside mixing zone, max.	160 µg/L	
	30-day average	7.2 µg/L	
	Coldwater inside mixing zone, max.	320 µg/L	
	Limited Resource warm water		
	Outside mixing zone, max.	160 µg/L	
	Inside maximum zone, max.	320 µg/L	
	Groundwater Quality Standards		CELDs 1994
CO	Human Health	7,000 µg/L	
NC	Water Quality Standards (drinking water supply)		
	Class GS waters	7.0 mg/L	
WI	Public Human Health		
	Enforcement standard	7 mg/L	
	Preventive Action Limit	0.7 mg/L	
VT	Enforcement standard	7.5 mg/L	VANR 1988
	Preventive action limit	3.5 mg/L	
	Hazardous Constituents		CELDs 1994
NJ	Listed as hazardous substance (in relation to drinking water systems)	Yes	
VT	Hazardous waste from non-specific sources. Vermont listed wastes (VT08) "waste ethylene glycol based coolants, antifreezes, and solutions containing greater than 700 ppm of ethylene glycol" toxic waste	Yes	

ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FSTRAC = Federal-State Toxicology and Regulatory Alliance Committee; IRIS = Integrated Risk Information System; MCL = Maximum Contaminant Level; NRC/NAS = National Research Council/National Academy of Sciences; OAR = Office of Air and Radiation; OERR = Office of Emergency and Remedial Response; OPTS = Office of Pesticides and Toxic Substances; OSW = Office of Solid Wastes; OW = Office of Water; RfD = Reference Dose; SNARL = Suggested No Adverse Response Level; SOCMI = Synthetic Organic Chemicals Manufacturing Industry; VOC = Volatile Organic Compound; WHO = World Health Organization

Table 7-2. Regulations and Guidelines Applicable to Propylene Glycol

Agency	Description	Information	References
INTERNATIONAL			
WHO	Acceptable Daily Intake	0-25 mg/kg	FAO/WHO 1974
NATIONAL			
Regulations:			
a. Air			
EPA OAR	App. A - Chemicals Defining Synthetic Organic Chemical and Polymer Manufacturing	Yes	40 CFR 52 EPA 1972a
	Subpart VV - Std. of Performance for Equipment Leaks of VOC in SOCMI: Chemicals Produced by Affected Facilities	Yes	40 CFR 60.489 EPA 1983
	Definitions of Emissions from Polymer Manufacturers: Definition of "Polymerization Reaction Section"	Yes	40 CFR 60.561 EPA 1990b
	Subpart NNN - Std. of Performance for VOC Emissions from SOCMI Distillation Operations: Chemical Affected	Yes	40 CFR 60.667 EPA 1990b
	Subpart RRR - Std. of Performance for VOC Emissions from SOCMI Process Reactors: Chemicals Affected	Yes	40 CFR 60.707 EPA 1993b
	New Source Performance Standard	Yes	58 FR 45962 EPA 1993c
b. Water			
EPA OW	Bulk Organic Chemicals Under the Clean Water Act	Yes	40 CFR 414.70 EPA 1987d
	App. A - Non-Complexed Metal-bearing Waste	Yes	40 CFR 414 EPA 1987d
EPA OWRS	Pesticide subject to registration and reregistration	Yes	40 CFR 152.146 EPA 1989b EPA 1989a
c. Food:			
FDA	Generally Recognized as Safe	Yes	21 CFR 184.1666 FDA 1982
	2,4-D: Food Tolerances for Residues 2,4-D Applied in the Form of Polyethylene Glycol and/or Propylene Glycol		40 CFR 180.142 EPA 1982
	Max. 2,4-D tolerance: Pasture and Rangeland Grasses	1000 ppm	
	Min. 2,4-D tolerance: Blueberries and Rice	0.1 ppm	
	Inert Ingredients Exempt From Tolerances	Yes	40 CFR 180.1001 EPA 1971
d. Other:			
EPA OPTS	Temperature Correction Factors for Organic Solvents	0.043 K°C/mmHg	40 CFR 796.1220 EPA 1985a

Table 7-2. Regulations and Guidelines Applicable to Propylene Glycol (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Avian Dietary Testing Procedures - Sample Diluents	Yes	40 CFR 797.2050 EPA 1985b
	Sample Diluents for Bobwhite Reproductive Tests	Yes	40 CFR 797.2130 EPA 1985b
	Sample Diluents for Mallard Reproductive Tests	Yes	40 CFR 797.2150 EPA 1985b
	Sample Carriers for Avian Acute Toxicity Test	Yes	40 CFR 797.2175 EPA 1985b
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable ambient air concentrations		
VA	24 hours	1.10×10^3 µg/m^3	NATICH 1991

EPA = Environmental Protection Agency; FDA = Food and Drug Administration; NATICH = National Air Toxics Information Clearinghouse; OAR = Office of Air and Radiation; OPTS = Office of Pesticides and Toxic Substances; OW = Office of Water; OWRS = Office of Waste Regulations and Standards; SOCMI = Synthetic Organic Chemical Manufacturing Industry; VOC = Volatile Organic Compound

8. REFERENCES

*Aarstad K, Dale O, Aakervik O, et al. 1993. A rapid gas chromatographic method for determination of ethylene glycol in serum and urine. J Anal Toxicol 17(4):218-221.

*Abbondandolo A, Bonatti S, Corsi C, et al. 1980. The use of organic solvent in mutagenicity testing. Mutat Res 79:141-150.

*Abe S, Sasaki M. 1982. SCE as an index of mutagenesis and/or carcinogenesis. Chapter 24 In: Sister chromatid exchange. Prog Top Cytogenet 2:461-514.

*Aberer VW, Fuchs T, Peters K-P, et al. 1993. Propylene glycol: Cutaneous side effects and test methods. Literature and results of a multicenter study of the German contact allergy group (DKG). Dermatosen 41:25-27. [German]

*Aboul-Enein HY, Islam MR. 1989. High performance liquid chromatography determination of ethylene glycol in stamp pad ink. Toxicol Environ Chem 24(3):181-184.

*ACGIH. 1994. Threshold limit values and biological exposure indices for 1994-1995. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

*Adams M, Collins M. 1988. Sensitive portable gas chromatograph with data retrieval and communications capability for remote surveillance of toxic gases and vapours in plant. Analytical Proceedings 25(6):190-191.

Adams WH, Toal RL, Breider MA. 1991. Ultrasonographic findings in dogs and cats with oxalate nephrosis attributed to ethylene glycol intoxication: 15 cases (1984-1988). J Am Vet Med Assoc 199(4):492-496.

Adams WH, Toal RL, Walker MA, et al. 1989. Early renal ultrasonographic findings in dogs with experimentally induced ethylene glycol nephrosis. Am J Vet Res 50(8):1370-1376.

Agren-Jonsson S, Magnusson B. 1976. Sensitization to propantheline bromide, trichlorocarbanilide and propylene glycol in an antiperspirant. Contact Dermatitis 2(2):79-80.

*Ahluwalia P, Amma MKP, Sareen K. 1980. Propane 1,2-diol induced in vivo and in vitro changes in rat erythroeytes. Ind J Exp Biol 18:382-284.

Ahmed MM. 1971. Ocular.effects of antifreeze poisoning. Br J Ophthalmol 55(12):854-855.

AIHA. 1985. Propylene glycol. American Industrial Hygiene Association. Akron, OH, 5.

Ambrose D, Hall DJ. 1981. Thermodynamic properties of organic oxygen compounds: I. The vapor pressures of 1,Zethanediol (ethylene glycol) and bis(2-hydroxyethyl)ether (diethylene glycol). J Chem Thermodyn 13:61-66.

*Cited in text

8. REFERENCES

Amoozegar A, Warrick AW, Fuller WH. 1986. Movements of selected organic liquids into dry soils. Hazardous Waste and Hazardous Materials 3:29-41.

Amstrup SC, Gardner C, Myers KC, et al. 1989. Ethylene glycol (antifreeze) poisoning in a free-ranging polar bear. Vet Hum Toxicol 31(4):317-319.

Anbar M, Neta P. 1967. A compilation of specific bimolecular rate constants for the reactions of hydrated electrons, hydrogen atoms, and hydroxyl radicals with inorganic and organic compounds in aqueous solution. Int J Appl Rad Isotopes 18:493-523.

*Andersson K, Levin J-O, Lindahl R, et al. 1982. Sampling of ethylene glycol and ethylene glycol derivatives in work-room air using Amberlite XAD resins. Chemosphere 1 l(11): 1115 1119.

*Andersson K, Levin J-O, Lindahl R, et al. 1984. Influence of air humidity on sampling efficiency of some solid adsorbents used for sampling organics from work-room air. Chemosphere 13(3):437-444

Andrews LS, Snyder R. 1986. Toxic effects of solvents and vapors. In: Klaassen CD, Amdur MO, Doull J, eds. Cassarett and Doull's toxicology: The basic science of poisons. 3rd ed. New York, NY: MacMillan Publishing Co., 654-657.

*Angelini G, Meneghini CL. 198 1. Contact allergy from proplene glycol. Contact Dermatitis 7:197-198.

Anonymous. 1970. Determination of the ethyl alcohol, isopropyl alcohol and propylene glycol content of essences and tinctures. Flavour Industry 1:313-3 15.

*Anonymous. 1987. Ethylene glycol intoxication due to contamination of water systems. Atlanta, GA: Centers for Disease Control, Morbidity and Mortality Weekly Report 36(36):611-614.

AOAC. 1985. Official methods of analysis. 10th ed. and supplements. Washington, DC: Association of Official Analytical Chemists.

*Apple FS, Googins MK, Resen D. 1993. Propylene glycol interference on gas-chromatographic assay of ethylene glycol. Clinical Chemistry 39:167.

*Arulanantham K, Gene1 M. 1978. Central nervous system toxicity associated with ingestion of propylene glycol. J Pediatr 93:5 15-5 16.

*ASTER. 1995a. Assement Tools for the Evaluation of Risk. ASTER output for propylene glycol. U. S. Environmental Protection Agency.

*ASTER. 1995b. Assement Tools for the Evaluation of Risk. ASTER output for ethylene glycol. U. S. Environmental Protection Agency.

Atkinson R. 1985. Kinetics and mechanisms of the gas-phase reactions of hydroxyl radical with organic compounds under atmospheric conditions. Chem Rev 8569-201.

8. REFERENCES

Atkinson R. 1987. A structure-activity relationship for the estimation of rate constants for the gas-phase reactions of OH radicals with organic compounds. International Journal of Chemical Kinetics 19:799-828.

Atkinson R. 1989. Kinetics and mechanisms of the gas-phase reactions of the hydroxyl radical with organic compounds. Journal of Physical and Chemical Referenced Data Monograph 1.

*ATSDR. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles. Agency for Toxic Substances and Disease Registry, Division of Toxicology, Atlanta, GA.

*ATSDR/CDC. 1990. Subcommittee report on biological indicators of organ damage. Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Atlanta, GA.

Aungst BJ, Blake JA, Hussain MA. 1990. Contributions of drug solubilization, partitioning, barrier disruption, and solvent permeation to the enhancement of skin permeation of various compounds with fatty acids and amines. Pharmaceutical Research 7(7):712-718.

Balikova M, Kohlicek J. 1988. Rapid determination of ethylene glycol at toxic levels in serum and urine. Journal of Chromatography 434:469-474.

*Ball NA. 1984. Determination of ethylene oxide, ethylene chlorohydrin and ethylene glycol in aqueous solutions and ethylene oxide residues in associated plastics. J Pharm Sci 73(9):1305-1307.

*Ballarin C. 1980. [Studies on the identification of pharmacopeial glycols by thin-layer chromatography.] Pharm Prax 35260-264. (German)

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Phannacol 8471486.

Battersby NS, Wilson V. 1989. Survey of the anaerobic biodegradation potential of organic chemicals in digesting sludge. Appl Environ Microbial 55(2):433-439.

*Baud FJ, Bismuth C, Gamier R, et al. 1987. 4-Methylpyrazole may be an alternative to ethanol therapy for ethylene glycol intoxication in man. J Toxicol Clin Toxicol 24(6):463-483.

*Baud FJ, Galliot M, Astier A, et al. 1988. Treatment of ethylene glycol poisoning with intravenous 4-methylpyrazole. N Engl J Med 319(2):97-100.

Bauer MC, Weiss DJ, Perman V. 1991. Hematologic alterations in adult cats fed 6 or 12% propylene glycol. American Journal of Veterinary Research 53:69-72.

*Bauer MC, Weiss DJ, Perman V. 1992. Hematological alterations in kittens induced by 6 and 12% dietary propylene glycol. Vet Hum Toxicol 34(2):127-131.

*Beckett SD, Shields RP. 1971. Treatment of acute ethylene glycol (antifreeze) toxicosis in the dog. J Amer Vet Med Assoc 158(4):472-476.

8. REFERENCES

Bedard RG. 1976. Biodegradability of organic compounds. Master of Science Thesis, Connecticut University, Storrs, Connecticut. Prepared for Office of Water Research and Technology, Washington, DC. NTIS no. PB-264707.

*Berger JR, Ayyar DR. 1981. Neurological complications of ethylene glycol intoxication. Arch Neurol 38:724-726.

Bidmon HJ, Pitts JD, Solomon I-IF, et al. 1990. Estradiol distribution and penetration in rat skin after topical application, studied by high resolution autoradiography. Histochemistry 95(1):43-54.

*Bieszkiewicz E, Van Hoi D, Matusiak K. 1979. Effects of methyl alcohol and ethylene glycol on the work of activated sludge. Acta Microbial Pol 28(3):255-260.

*Blakeley KR, Rinner SE, Knochel JP. 1993. Survival of ethylene glycol poisoning with profound acidemia. New England Journal of Medicine 328(7):515-516.

*Blandford DE, Desjardins PR. 1994. A rapid method for measurement of ethylene glycol. Clinical Biochemistry 27(1):25-30.

*Blomstrom DC, Beyer EM. 1980. Plants metabolise ethylene to ethylene glycol. Nature 283(5742):66-68.

*Blood FR. 1965. Chronic toxicity of ethylene glycol in the rat. Food Cosmet Toxicol 3:229-234.

Blood FR, Elliot GA, Wright MS. 1962. Chronic toxicity of ethylene glycol in the monkey. Toxicol Appl Pharmacol 4:489-49 1.

Boatman RJ, Cunningham SL, Ziegler DA. 1986. A method for measuring the biodegradation of organic chemicals. Environ Toxicol Chem 5:233-243.

Boer-mans HJ, Ruegg PL, Leach M. 1988. Ethylene glycol toxicosis in a pygmy goat. J Am Vet Med Assoc 193(6):694-696.

Bogusz M. 1980. Vitreous humour as reliable material for ethanediol determinations. Forensic Sci Int 16(1):75-76.

*Bogusz M, Bialka J, Gierz J, et al. 1986. Rapid determination of ethylene glycol in biological material. Z Rechtsmed 96(1):23-26.

Bolbot JA, Anthony C. 1980. The metabolism of 1,2-propanediol by the facultative methylotroph pseudomnas AMl. J Gen Microbial 120:245-254.

*Bond GG, Shellenberger RJ, Flores GH, et al. 1985. A case-control study of renal cancer mortality at a Texas chemical plant. Am J Ind Med 7(2):123-139.

Bonitenko I, Kutsenko SA, Koposov ES, et al. 1990. [Acute poisoning with ethylene glycol esters.] Klin Med 68:126-130. (Russian)

8. REFERENCES

*Borgerding MF, Milhous LA Jr, Hicks RD, et al. 1990. Cigarette smoke composition: Part 2. Method for determining major components in smoke of cigarettes that heat instead of bum tobacco. J Assoc Off Anal Chem 73(4):610-615.

Bost RO, Sunshine I. 1980. Ethylene glycol analysis by gas chromatography. J Anal Toxicol 4(2):102-103.

Boublik T, Fried V, Hala E. 1973. The vapour pressures of pure substances: Selected values of the temperature dependence of the vapour pressures of some pure substances in the normal and low pressure region. New York, NY: Elsevier Scientific Publishing Company, l-5, 99, 119.

Boyd RD, Haworth C, Stacey TE, et al. 1976. Permeability of the sheep placenta to unmetabolized polar non-electrolytes. J Physiol 256(3):617-634.

*Brazeau GA, Fung JL. 1990. Mechanisms of creatine kinase release from isolated rat skeletal muscles damaged by propylene glycol and ethanol. J Pharm Sci 79(5):393-397.

*Brega AA, Quadri P, Villa ,et al. 1992. Improved HPLC determination of plasma and urine oxalate in the clinical diagnostic laboratory. Journal of Liquid Chromatography 15(3):501-511.

Bridie A, Wolff CJM, Winter M. 1979. BOD and COD of some petrochemicals. Water Research 13:627-630.

Bronaugh RL, Franz TJ. 1986. Vehicle effects on percutaneous absorption: In vivo and in vitro comparisons with human skin. Lipids 21(5):309-314.

Brown DJ, Jain NC, Fomey RB, et al. 1968. Gas chromatographic assay of glycol-ethanol combinations in biological materials. J Forensic Sci 13(4):537-543.

*Browning E. 1965. Toxicity and metabolism of industrial solvents. New York, NY: American Elsivier, 594-600, 642-644.

*Capo MA, Sevil MB, Lopez ME, et al. 1993. Ethylene Glycol action on neurons and its cholinomimetic effects. Journal of Environmental Pathology, Toxicology and Oncology. 12(3):155-159.

*Carney E, Liberacki A, Bartels M, et al. 1995. Identification of proximate toxicant for ethylene glycol developmental toxicity using rat whole embryo culture. The Toxicologist 15(1):163.

*Casazza JP, Fretas J, Stambuk D, et al. 1987. The measurement of 1,2Propanediol, D, L-2,3-Butanediol and Meso-2,3-Butane&o1 in controls and alcoholic cirrhotics. Alcohol,& Alcohoism Suppl 1, 607-609.

Caskey WH, Taber WA. 1981. Oxidation of ethylene glycol by a salt-requiring bacterium. Appl Environ Microbial 42(1): 180-l 83.

*Castle L, Cloke HR, Crews C, et al. 1988a. The migration of propylene glycol, mono-, di-, and triethylene glycols from regenerated cellulose film into food. Z Lebensm Unters Forsch 187(5):463-467.

8. REFERENCES

*Castle L, Cloke HR, Star-tin Jr, et al. 1988b. Gas chromatographic determination of monoethylene glycol and diethylene glycol in chocolate packaged in regenerated cellulose film. J Assoc Off Anal Chem 7 1(3):499-502.

Catanzaro JM, Smith JG Jr. 1991. Propylene glycol dermatitis. J Am Acad Dermatol 24(1):90-95.

Cate JC, Hedrick R. 1980. Propylene glycol intoxication and lactic acidosis. N Engl J Med 303:1237.

*CELDs. 1994. Computer-assisted Environmental Legislative Database. University of Illinois at Urbana.

*Chemical and Engineering News. 1994. Organics led last years top 50 chemicals production increase. 13.

*Cheng JT, Beysolow TD, Kaul B, et al. 1987. Clearance of ethylene glycol by kidneys and hemodialysis. J Toxicol Clin Toxicol 25(1-2):95-108.

Cheng YS, Marshall TC, Kanapilly GM. 1982. Generation and characterization of ethylene glycol vapors and aerosols. Am Ind Hyg Assoc J 43(4):250-253.

Cheung ST, Lin WN. 1987. Simultaneous determination of methanol, ethanol, acetone, isopropanol and ethylene glycol in plasma by gas chromatography. J Chromatogr 414(1):248-250.

Child J, Willetts A. 1978. Microbial metabolism of aliphatic glycols: Bacterial metabolism of ethylene glycol. Biochim Biophys Acta 538(2):316-327.

Chou JY, Richardson KE. 1978. The effect of pyrazole on ethylene glycol toxicity and metabolism in the rat. Toxicol Appl Pharmacol 43(1):33-44.

Chou WL, Speece RE, Siddiqi RH. 1979. Acclimation and degradation of petrochemical wastewater components by methane fermentation. Biotechnol Bioeng Symp 8:391-414.

Christian KL, Moorehead WP. 1985. Ethylene dichloride/ethylene glycol spill in a major water resource in British Columbia. J Environ Health 47:192-196.

Christopher MM, Eclcfeldt JH, Eaton JW. 1990a. Propylene glycol ingestion causes D-lactic acidosis. Lab Invest 62:114-118.

*Christopher MM, Eckfeldt JH, Eaton JW. 1990b. Propylene glycol ingestion causes D-lactic acidosis. Laboratory Investigation. 62(1): 114-118.

*Christopher MM, Perman V, Eaton JW. 1989a Contribution of propylene glycol-induced Heinz body formation to anemia in cats. J Am Vet Med Assoc 194(8):1045-1056.

Christopher MM, Perman V, White JG, et al. 1989b. Propylene glycol-induced Heinz body formation and D-lactic acidosis in cats. Prog Clin Biol Res 319:69-92.

8. REFERENCES

*Chum A, Amma MKP. 1985. Changes in the hepatic carbohydrate metabolism of propane- 1,2 diol fed rats. IRCS Med Sci 13:958.

*Chung PK, Tuso P. 1989. Cerebral computed tomography in a stage IV ethylene glycol intoxication. Conn Med 53(9):513-514.

*Clark .CR, Marshall TC, Merickel BS, et al. 1979. Toxicological assessment of heat transfer fluids proposed for use in solar energy applications. Toxicol Appl Pharmacol 5 1:529-535.

*Clay KL, Murphy RC. 1977. On the metabolic acidosis of ethylene glycol intoxication. Toxicol Appl Pharmacol 39:39-49.

*CMR. 1990. Chemical profile: Ethylene glycol. Chemical Marketing Reporter, New York, NY.

Colwell RR, Sayler GS. 1978. Microbial degradation of industrial chemicals. Water Pollut Microbial 2:111-134.

*Commens CA. 1990. Topical propylene glycol and hyperosmolarity. Br J Dermatol 122(1):77-80.

Conway RA, Waggy GT, Spiegel MH, et al. 1983. Environmental fate and effects of ethylene oxide. Environ Sci Technol 17(2):107-112.

Coon RA, Jones RA, Jenkins LJ Jr, et al. 1970. Animal inhalation studies of ammonia, ethylene glycol, formaldehyde, dimethylamine, and ethanol. Toxicol Appl Pharmacol 16646-655.

*Corazza M, Virgili A, Mantovani L, et al. 1993. Propylene glycol allergy from acyclovir cream with cross-reactivity to hydroxypropyl cellulose in a transdermal estradiol system? Contact Dermatitis 29(5):283-284.

Costa J, Soley J, Mata J, et al. 1985. Biodegradation of ethylene glycol. Effluent and Water Treatment Journal 25(12):429-434.

Cox DP. 1978. The biodegradation of polyethylene glycols. Adv Appl Microbial 23:173-193.

Crowell WA, Whitlock RH, Stout RC, et al. 1979. Ethylene glycol toxicosis in cattle. Cornell Vet 69(3):272-279.

Cucuzzella A. 1992. Ethylene glycol poisoning. J Gen Intern Med 7(4):467.

Curnmings KC, Jatlow PI. 1982. Sample preparation by ultra-filtration for direct gas-chromatographic analysis of ethylene glycol in plasma. J Anal Toxicol 6(6):324-326.

*Cunningham KM, Goldberg MC, Weiner ER. 1985. The aqueous photolysis of ethylene glycol adsorbed on goethite. Photochem Photobiol 41(4):409-416.

*Damien M, Luciano AA, Peluso JJ. 1989. Propanediol-induced alterations in membrane intergrity, metabolism and developmental potential of mouse zygotes. Human Reproduction 4(8):969-974.

8. REFERENCES

*Damien M, Luciano AA, Peluso JJ. 1990. Propanediol alters intracellular pH and developmental potential of mouse zygotes independently of volume change. Human Reproduction 5(2):212-216.

*Danielson JW, Snell RP, Oxborrow GS. 1990. Detection and quantitation of ethylene oxide, 2-chloroethanol, and ethylene glycol with capillary gas chromatography. J Chromatogr Sci 28:97-101.

*Daubert TE, Danner RP. 1980. Data compilation: Tables of physical and thermodynamic properties of pure compounds. American Institute of Chemical Engineers, Design Institute for Physical Property Data Project 801, The Pennsylvania State University.

Daubert TE, Danner RP. 1985. Data compilation tables of properties of pure compounds. New York, NY: Design Institute for Physical Property Data, American Institute of Chemical Engineers, 450.

*Daubert TE, Danner RP. 1989. Physical and thermodynamic properties of pure chemicals: Data compilation. Design Institute for Physical Property Data, American Institute of Chemical Engineers. New York, NY: Hemisphere Pub Corp, 4 vol.

*Dean ME, Stock BH. 1974. Propylene glycol as a drug solvent in the study of hepatic microsoma] enzyme metabolism in the rat. Toxicol Appl Pharmacol 2844-52.

Demey HE, Daelemans R.A, Verpooten GA, et al. 1988. Propylene glycol-induced side effects during intravenous nitroglycerin therapy. Intensive Care Med 14(3):221-226.

*Denning DW, Webster DB. 1987. Detrimental effect of propylene glycol on natural killer cell and neutrophil function. J Pharm. Pharmacol. 39:236-238.

*DePass LR, Frank FR, Weaver EV, et al. 1984. Ethylene glycol: Twenty-four month oncogenicity feeding study in mice. Bushy Run Research Center. Report 46-89.

*DePass LR, Garman RH, Woodside MD, et al. 1986a. Chronic toxicity and oncogenicity studies of ethylene glycol in rats and mice. Fundam Appl Toxicol 7(4):547-565.

*DePass LR, Woodside MD, Maronpot RR, et al. 1986b. Three-generation reproduction and dominant lethal mutagenesis studies of ethylene glycol in the rat. Fundam Appl Toxicol 7(4):566-572.

*DeRudder D, De Graeve E, Van Severen R, et al. 1986. Quantification of ethylene chlorohydrin and ethylene glycol as potential reaction products in gas-sterilized medical-grade plastics. J Clin Hosp Pharm 11(2):125-130.

*Dial SM, Thrall MA, Harmar DW. 1989. 4methylpyrazole as treatment for naturally acquired ethylene glycol intoxication in dogs. J Am Vet Med Assoc 195(1):73-76.

*Dial SM, Thrall MAH, Harmar DW. 1994. Efficacy of 4-methylpyrazole or treatment of ethylene glycol intoxication in dogs. Am J Vet Res 55(12): 1762-1770.

*Diamandis EP, Efstathiou CE, Hadjiioannou TP. 1980. Automatic determination of ethylene glycol in anti-freeze solutions with a periodate-sensitive flow-through electrode. Analyst 105(1257):1203-1207.

8. REFERENCES

*Dorman DC, Haschek WM. 1991. Fatal propylene glycol toxicosis in a horse. J Am Vet Med Assoc 198(9):1643-1644.

*Drajun J. 1991. Geochemistry and soil chemistry reactions occurring during in situ vitrification. J Hazardous Materials 26:343-364.

*Driver J, Tardiff RG, Sedik L, et al. 1993. In vitro percutaneous absorption of [14C] ethylene glycol. J Expo Anal Environ Epidemiol 3(3):277-284.

*Dwyer DF, Tiedje JM. 1983. Degradation of ethylene glycol and polyethylene glycols by methanogenic'consortia. Appl Environ Microbial 46(1): 185 190.

*Ebisuno S, Morimoto S, Yoshida T, et al. 1987. Effect of dietary calcium, and magnesium, on experimental renal tublar deposition of calcium oxalate crystal induced by ethylene glycol administration and its prevention with phytim and citrate. Urol Int 42:330-337.

Eckfeldt JH, Light RT. 1980. Kinetic ethylene glycol assay with use of yeast alcohol dehydrogenase. Clin Chem 26(9):1278-1280.

*Edinboro LE, Nanco CR, Soghioan DM, et al. 1993. Determination of ethylene glycol in serum utilizing direct injection on a wide-bore capillary column. Therapeutic Drug Monitoring 15:220-223.

Eichbaum FW, Yasaka WJ. 1976. Antiarrhythmic effect of solvents: Propylene glycol, benzyl alcohol. Basic Res Cardiol 71(4):355-370.

Eisenreich SJ, Looney BB, Thornton JD. 1981. Airborne organic contaminants in the Great Lakes ecosystem. Environ Sci Technol 15(1):30-38.

*EPA. 197 1. Tolerances and exemptions from tolerances for pesticide chemicals in or on raw agricultural commodities. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 180.1001.

*EPA. 1972a. Approval and promulgation of implementation plans. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 52.

EPA. 1972b. Anaerobic treatment of synthetic organic wastes. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Monitoring.

EPA. 1976. Frequency of organic compounds identified in water. Athens, GA: U.S. Environmental Protection Agency, Office of Research and Development, Environmental Research Laboratory.

EPA. 1977a. An index of refractory organics. Ada, OK: U.S. Environmental Protection Agency, Office of Research and Development, Robert S. Kerr Environmental Laboratory.

EPA. 1977b. Industrial process profiles for environmental use: Chapter 6. The industrial organic chemicals industry. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development, Industrial Environment Research Laboratory. EPA-600/2-77-023f.

8. REFERENCES

EPA. 1978. Ethylene oxide, ethylene chlorohydrin, and ethylene glycol: Proposed ,maximum residue limits and maximum levels of exposure. Washington, DC: U.S. Environmental Protection Agency. Federal Register 43:27474-27483.

*EPA. 1979. Investigation of selected potential environmental contaminants: Ethylene glycol, propylene glycols and butylene glycols. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. EPA/56011 l-79-00.

EPA. 1980. Ethylene. glycol. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Emissions Standards and Engineering Division. EPA-450/3-80-028d.

*EPA. 1982. Tolerances and exemptions from tolerances for pesticide chemicals in or on raw agricultural commodities. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 180.142.

*EPA. 1983. Standards of performance for new stationary sources. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 60.489.

EPA. 1984a. CC/MS analysis of organics in drinking water concentrates and advanced waste treatment concentrates. Volume I: Analysis results for 17 drinking water, 16 advanced waste treatment and 3 process blank concentrates. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, Health Effects Research Laboratory. EPA-600/l-84-020A.

*EPA. 1984b. Premanufacture notification exemptions: polymers. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 723.250.

*EPA. 1985a. Temperature corrections for organic solvents. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 796.1220.

*EPA. 1985b. Environmental effects testing guidelines. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 797.

*EPA. 1987a. Health and environmental effects document for propylene glycol. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

*EPA. 1987b. Toxic chemical release reporting: Community right to know. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65.

*EPA. 1987c. Toxic chemical release reporting: Community right to know. U.S. Environmental Protection Agency. Federal Register 52(107):21152-21177.

*EPA 1987d. Organic chemicals, plastics, and synthetic fibers. U.S. Environmental Protection . Agency. Code of Federal Regulations. 40 CFR 414.

*EPA. 1989a. Pesticides required to be reregistered: List C. U.S. Environmental Protection Agency. Federal Register 54(140):30846-30855.

8. REFERENCES

*EPA. 1989b. Reregistration. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 152.146.

*EPA. 1990a. Interim methods for development of inhalation reference doses. Washington, DC: U.S. Environmental Protection Agency. EPA/600/890/066A.

*EPA. 1990b. Standards of performance for new stationary sources. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 60.

*EPA. 1993a. Reportable quantity adjustments. U.S. Environmental Protection Agency. Federal Register. 58 FR 54836.

*EPA. 1993b. Standards of performance for new stationary sources. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 60.707.

*EPA. 1993c. New source performance standards. U.S. Environmental Protection Agency. Federal Register. 58 FR 45962.

*EPA. 1995a. Test methods for evaluating solid waste. Method 8015b, revision 2, January 1995 “Nonhalogenated Organics Using GCIFTD SW 846.

*EPA. 1995b. Test methods for evaluating solid waste; Method 8430 revision 0 January 1995; “Nonhalogenated Organics Using GCLFID SW 846.

*EPA 1995c. Toxic Chemical release inventory reporting form R and instructions. Office of Pollution, Prevention and Toxics. Washington DC EPA 745-K-95-051.

*Eun HC, Kim YC. 1989. Propylene glycol allergy from ketoconazole cream. Contact Dermatitis 21(4):274-275.

*Evans WH David EJ. 1974. Biodegradation of mono-, di-, and triethylene glycols in river waters under contrdlled laboratory conditions. Water Research 8(2):97-100.

*Evans WH, Dennis A. 1973. Spectrophotometric determination of low levels in mono-, di-, and triethylene glycols in surface waters. Analyst 98(1172):782-79 1.

Evmiridis NP. 1989. Periodate determination by FIA with chemiluminescence emission detection, and its application to ethylene glycol (ethanediol). Talanta 36(3):357-362.

*Factor SA, Lava NS. 1987. Ethylene glycol intoxication: A new stage in the clinical syndrome. NY State J Med 87(3):179-180.

*FAO/WHO. 1974. Toxicological evaluation of certain food additives with a review of general principles and of specifications. In: 17th Report of the Joint FAOAVHO Expert Committee on Food Additives, Geneva, Switzerland, June 25-July 4, 1973. Geneva, Switzerland: Food and Agricultural Organization of the United Nations/World Health Organization.

8. REFERENCES

Farsund T. 1978. Cell kinetics of mouse urinary bladder epithelium: VI. Changes in the proportions of cells with various nuclear DNA content after repeated doses of propylene glycol (1, 2-propanediol). Virchows Arch [B] 27(1): l-6.

FDA. 1973. Teratologic evaluation of compound FDA 7 1-56 (propylene glycol) in mice, rats, hamsters, and rabbits. PB-223-822.

FDA. 1974. Mutagenic evaluation of compound FDA 71-56 (propylene glycol). PB-245450.

*FDA. 1977a. Indirect food additives: Adhesives and components of coatings. Food and Drug Administration. Code of Federal Regulations. 21 CFR 175.105.

*FDA. 1977b. Indirect food additives: Adhesive coatings and components. Food and Drug Administration. Federal Register 42(50):14534-14554.

FDA. 1977c. Propylene Glycol and Propylene Glycol Monostearate. Food and Drug Administration. Federal Register 42(117):30865-30866.

*FDA. 1982. Generally recognized as safe. Food and Drug Administration. Code of Federal Regulations. 21 CFR 184.1666.

*FEDRIP. 1994. Federal Research in Progress. Dialog Information Service, Inc., Amarillo, TX.

*FEDRIP. 1995. Federal Research in Progress. Dialog Information Service, Inc., Amarillo. TX.

Fincher EL, Payne WJ. 1962. Bacterial utilization of ether glycols. Appl Microbial 10:542-547.

Flanagan RJ, Dawling S, Buckley BM. 1987. Measurement of ethylene glycol in biological specimens using derivatization and gas-liquid chromatography with flame ionization detection. Ann Clin Biochem 24(1):80-84.

*Fligner CL, Jack R, Twiggs GA, et al. 1985. Hyperosmolality induced by propylene glycol: A complication of silver sulfadiazine therapy. J Amer Med Assoc 253(11):1606-1609.

*Florida. 1994. Personal conversation with G. Robbins to Marion Deerhake, Research Triangle Institute, regarding air quality guidelines. Florida Pine&s County Air Quality Office (9/29/94).

*Fait FF Jr, Cowell RL, Brobst DF, et al. 1985. X-ray powder diffraction and microscopic analysis of crystalluria in dogs with ethylene glycol poisoning. Am J Vet Res 46(11):2404-2408.

Fox LE, Grauer GF, Dubielzig RR, et al. 1987. Reversal of ethylene glycol-induced nephrotoxicosis in a dog. J Am Vet Med Assoc 191(11):1433-1435.

*Frantz SW, Beskitt JL, Grosse CM, et al. 1989. Ethylene glycol: Comparison of pharmacokinetics and material balance following single intravenous, oral and cutaneous administration to male and female Sprague-Dawley rats. Bushy Run Research Center, Union Carbide Corp., Report No. 51-543.

8. REFERENCES

*Frantz SW, Tallant MJ, Beskitt JL. 1991. Ethylene glycol: comparisons of pharmacokinetic and material balance studies following single intravenous, peroral, and percutaneous administrations to female CD-l mice. Bushy Run Research Center, Union Carbide Corp., Report No. 53-550.

*Fraser AD, MacNeil W. 1993. Calorimetric and gas chromatographic procedures for glycolic acid in serum: the major toxic metabolite of ethylene glycol. Clinical Toxicology 31(3):397-405.

*Freitag D, Ballhom L, Geyer H, et al. 1985. Environmental hazard profile of organic chemicals: An experimental method for the assessment of the behaviour of organic chemicals in the ecosphere by means of simple laboratory tests with 14C labeled chemicals. Chemosphere 14(10):1589-1616.

Frosch PJ, Pekar U, Enzmann H. 1990. Contact allergy to propylene glycol: Do we use the appropriate test concentration ? Dermatol Clin 8(1):111-1113.

*FSTRAC. 1990. Summary of state and federal drinking water standards and guidelines. U.S. Environmental Protection Agency. Chemical Communication Subcommittee, Federal-State Toxicology and Regulatory Alliance Committee (FSTRAC).

Fuller EW Jr. 1969. Ethylene glycol: A review. Med Leg Bull 18(10):1-8.

*Gabow PA, Clay K, Sullivan JB, et al. 1986. Organic acids in ethylene glycol intoxication. Ann Intern Med 105(1):16-20.

*Gaston LW, Stadtman ER. 1963. Fermentation of ethylene glycol by Clostridium glycolicum. J Bacterial 85:356-362.

*Gaunt IF, Carpanin FMB, Grass0 P, et al. 1972. Long-term toxicity of propylene glycol in rats. Food Cosmet Toxicol 10(2):151-162.

Gebhardt DOE. 1986. The teratogenic action of propylene glycol (propanediol-1,2) and propanediol-1,3 in the chick embryo. Teratology 1:153-162.

Gerhold RM, Malaney GW. 1966. Structural determinants in the oxidation of aliphatic compounds by activated sludge. J Water Pollut Contr Fed.

*Gershoff SN, Andms SB. 1962. Effect of vitamin B6 and magnesium on renal disposition of calcium oxalate induced by ethylene glycol administration. Proceedings of the Society for Experimental Biology and Medicine 109:99-102.

*Giachetti C, Zanolo G, Assandri A, et al. 1989. Determination of cyclic butylboronate esters of some 1,2- and 2,3-diols in plasma by high-resolution gas chromatography/mass spectrometry. Biomedical and Environmental Mass Spectrometry 18(8):592-597.

*Glasgow AM, Boeckx RL, Miller MK, et al. 1983. Hyperosmolality in small Infants due to propylene glycol. Pediatrics 72(3):353-355.

*Godolphin W, Meagher EP, Sanders HD, et al. 1980. Unusual calcium oxalate crystals in ethylene glycol poisoning. Clin Toxicol 16(4):479-486.

8. REFERENCES

*Gonzalez CF, Taber WA, Zeitoun MA. 1972. Biodegradation of ethylene glycol by a salt-requiring bacterium. Appl Microbial 24(6):911-919.

*Gordon HL, Hunter JM. 1982. Ethylene glycol poisoning: A case report. Anaesthesia 17:332-338.

Grabinska-Loniewska A. 1974. Studies on the activated sludge bacteria participating in the biodegradation of methanol, formaldehyde and ethylene glycol: II. Utilization of various carbon and nitrogen compounds. Acta Microbial Pol Ser B Microbial Appl 6(2):83-88.

*Grafton TF, Hansen DK. 1987. In vitro embryotoxic effects of ethylene glycol in rats. Teratogenesis, Carcinogenesis, and Mutagenesis 7:483-489.

*Grauer GF, Thrall MA, Henre BA, et al. 1984. Early clinicopathologic findings in dogs ingesting ethylene glycol. Am J Vet Res 45(11):2299-2303.

*Grauer GF, Thrall MA, Henre BA, et al. 1987. Comparison of the effects of ethanol and 4-methylpyrazole on the pharmacokinetics and toxicity of ethylene glycol in the dog. Toxicol Lett 35(2-3):307-314.

*Griffiths AJF. 1979. Neurospora prototroph selection system for studying aneuploid production. Environ Health Perspect 3 1:75-80.

*Griffiths AJF. 1981. Neurospora and environmentally induced aneuploidy. Short-Term Tests Chem Carcinog 1981:187-199.

Grosjean D. 1990. Atmospheric chemistry of toxic contaminants: 2. Saturated aliphatics: Acetaldehyde, dioxane, ethylene glycol ethers, propylene oxide. Journal of the Air Waste Management Association 40(11):1522-1531.

Gupta RN. 1982. Liquid-chromatographic determination of ethylene glycol in plasma. Clin Chem 28(1):32-33.

Giisten H, Klasinc L, Marie D. 1984. Prediction of the abiotic degradability of organic compounds in the troposphere. Journal of Atmospheric Chemistry 2:83-94.

Haines JR, Alexander M. 1975. Microbial degradation of polyethylene glycols. Appl Microbial 29:621-625.

Hamano T, Mitsuhashi Y, Tanaka K, et al. 1984. Study of enzymic determination of food additives: II. Enzymic determination of propylene glycol in commercial foods. Agric Biol Chemical 48(10):2517-2521.

*Hannuksela M, F÷rstr÷m L. 1978. Reactions to peroral propylene glycol. Contact Dermatitis 4(1):41-45.

*Hannuksela M, Pirila V, Salo OP. 1975. Skin reactions to propylene glycol. Contact Dermatitis 1:112-116.

Hansson P. 1990. Kinetic enzymic assay for ethylene glycol. Clin Chim Acta 189(2):243-244.

8. REFERENCES

Hansson P, Masson P. 1989. Simple enzymatic screening assay for ethylene glycol (ethane-I ,2-diol) in serum. Clin Chim Acta 182(1):95-101.

Harada T, Nagashima Y. 1975. Utilization of alklyether compounds by soil bacteria. Journal of Fermentation Technology 53(4):218-222.

*Harris MW, Chapin RE, Lockhart AC, et al. 1992. Assessment of a short-term reproductive and developmental toxicity screen. Fundamental and Applied Toxicology 19(2):186-196.

*Hartman PA, Bowman PB. 1977. Simple GLC determination of ethylene oxide and its reaction products in drugs and formulations. J Pharm Sci 66(6):789-792.

Hatfield R. 1957. Biological oxidation of some organic compounds. Industrial and Engineering Chemistry 49: 192- 196.

*Hattori T, Maehashi H. 1993. Propylene glycol-induced skeletal muscle excitation. Food Chem Toxicol 3 1(9):647-650.

*HazDat. 1995. Database. Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA. August 21, 1995.

*Heckerling PS. 1987. Ethylene glycol poisoning with a normal anion gap due to occult bromide intoxication. Ann Emerg Med 16(12):1384-1386.

*Hebich, K. 1990a. Method 970.61; Propylene glycol in cosmetics. Official Methods of Analysis of the AOAC, 15th Edition. AOAC, Arlington, VA

*Helrich, K. 1990b. Method 97 1.02; Glycerol, propylene glycol, and triethylene glycol in cased cigarette cut filler and ground tobacco. Official Methods of Analysis of the AOAC, 15th Edition, AOAC, Arlington, VA.

*Helrich, K. 1990c. Method 947.09; Propylene glycol in vanilla extract. Official Methods of Analysis of the AOAC, 15th Edition, AOAC, Arlington, VA.

Hertz CD, Oxenford JL, Warner JS. 1990. Development of analytical method for compliance monitoring of ethylene glycol, n-hexane, methyl ethyl ketone, and formaldehyde in drinking water. Proc Water Qua1 Technol Conf 171651-665.

*Hewlett TP, Jacobsen D, Collins TD, et al. 1989. Ethylene glycol and glycolate kinetics in rats and dogs. Veterinary and Human Toxicology 3 l(2): 116- 120.

*Hewlett TP, McMartin KE, Lauro AJ, et al. 1986. Ethylene glycol poisoning: The value of glycolic acid determinations for diagnosis and treatment. J Toxicol Clin Toxicol 24(5):389-402.

*Hewlett TP, Ray AC, Reagor JC. 1983. Diagnosis of ethylene glycol (antifreeze) intoxication in dogs by determination of glycolic acid in serum and urine with high pressure liquid chromatography and gas chromatography-mass spectrometry. J Assoc Off Anal Chem 66(2):276-283.

8. REFERENCES

*Hine J, Mookejee PK. 1975. The intrinsic hydrophilic character of organic compounds: Correlations in terms of structural contributions. J Org Chem 40(3):292-298.

*Hodgson AT, Wooley JD, Daisey JM. 1993. Emissions of volatile organic compounds from new carpets measured in a large-scale environmental chamber. J Air and Waste Management Association 43:316-324.

Holman NW Jr, Mundy RL, Teague RS. 1979. Alkyldiol antidotes to ethylene glycol toxicity in mice. Toxicol Appl Pharmacol 49(2):385-392.

*Holopainen JK. 1992. Catch and sex ratio of Carabiae (Coleoptera) in pitfall traps filled with ethylene glycol or water. Pedobiologia 36:257-26 1.

*Hong HL, Canipe J, Jameson CW, et al. 1988. Comparative effects of ethylene glycol and ethylene glycol monomethyl ether exposure on hematopoiesis and histopathology in B6C3Fl mice. J Environ Pathol Toxicol Oncol 8(7):27-38.

*Horiuti K, Sakoda T, Takei M, et al. 1992. Effects of ethylene glycol on the kinetics of contraction on flash photolysis of caged ATP in rat psoas muscle fibres. J Muscle Res Cell Motil 13(2):199-205.

*House P, Chaussard J, Harry P, et al. 1993. Simultaneous determination of ethylene glycol, propylene glycol, 1,3-butylene glycol and 2,3-butylene glycol in human serum and urine by wide-bore column gas chromatography. J Chromatography 619:251-257.

*Howard PH, Boethling RS, Jarvis WF, et al, eds. 1991. Handbook of environmental degradation rates. Chelsea, MI: Lewis Publishers, Inc. 392-393.

*HSDB. 1995a. Ethylene glycol. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

*HSDB. 1995b. Propylene glycol. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda MD.

*Huff E. 1961. Metabolism of 1,2-propanediol. Biochim Biophys Acta 48:506-517.

*Huggon I, James I, Macrae D. 1990. Hyperosmolality related to propylene glycol in an infant treated with enoximone infusion. BMJ 301(6742):19-20.

Hughes RD, Gove CD, Williams R. 1991. Protective effects of propylene glycol, a solvent used pharmaceutically, against paracetamol-induced liver injury in mice. Biochem Pharmacol 42(3):710-713.

Hughes S, Meschi PL, Johnson DC. 1981. Amperometric detection of simple alcohols in aqueous solutions by application of a triple-pulse potential waveform at platinum electrodes. Anal Chim Acta 132:1-10.

Hughes TW, Tiemey DR, Khan ZS. 1979. Measuring fugitive emissions from petrochemical plants. Chemical Engineering Progress 75:35-39.

8. REFERENCES

*Hylander B, Karlsson K, Person H, et al. 1989. Death and chronic renal failure CFR in severe ethylene glycol EG intoxication. Kidney Int 35(1):228.

Introna F Jr, Smialek JE. 1989. Antifreeze (ethylene glycol) intoxications in Baltimore (Maryland, USA): Report of six cases. Acta Morpho1 Hung 37(3-4):245-264.

*IRIS. 1995. Integrated Risk Information System (IRIS). Online. Ethylene glycol and propylene glycol. U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, October 3, 1995.

*Iwinski G, Jenke DR. 1987. Determination of alcohols in pharmaceuticals by ion-exclusion chromatography. J Chromatogr 392:397-405.

*Jacobsen D, Hewlett TP, Webb R, et al. 1988. Ethylene glycol intoxication: Evaluation of kinetics and cr-ystalluria. Am J Med 84(1): 145- 152.

*Jacobsen D, McMartin KE. 1986. Methanol and ethylene glycol poisonings: Mechanism of toxicity, clinical course, diagnosis and treatment. Med Toxicol 1(5):309-334.

*Jacobsen D, Ovrebo S, Ostborg J, et al. 1984. Glycolate causes acidosis in ethylene glycol poisoning and is effectively removed by hemodialysis. Acta Med Stand 216:409-416.

Jacobsen D, Sebastian CS, Barron SK, et al. 1990. Effects of 4-methylpyrazole, methanol/ethylene glycol antidote, in healthy humans. J Emerg Med 8(4):455-461.

Jar-vie DR, Simpson D. 1957. Simple screening test for the emergency identification of methanol and ethylene glycol in poisoned patients. Clin Chem 36(11): 1957- 1961.

Jenkins LD, Cook KA, Cain RB. 1979. Microbial degradation of polyethylene glycols. J Appl Bacterial 47(1):75-85.

Johanson G. 1989. Analysis of ethylene glycol ether metabolites in urine by extractive alkylation and electron-capture gas chromatography. Arch Toxicol 63(2): 107- 111.

Johanson G, Michel I, Norback D, et al. 1989. Biological monitoring of exposure to ethylene glycol ethers. Arch Toxicol Suppl 13:108-l 11.

Jones AW, Nilsson L, Gladh A, et al. 1991. 2,3-Butanediol in plasma from an alcoholic mistakenly identified as ethylene glycol by gas-chromatographic analysis. Clin Chem 37(8):1453-1455.

Jones N, Watson GK. 1976. Ethylene glycol and polyethylene glycol catabolism by a sewage bacterium. Biochem Sot Trans 4(5):1-892.

*Jonsson JA, Eklund A, Molin L. 1989. Determination of ethylene glycol in postmortem blood by capillary gas chromatography. J Anal Toxicol 13(1):25-26.

*Kaiser RE, Rieder RI. 1987. Native ethylene glycol in wine: Application of a dead volume free, very fast “deans heart-cut” system on-line with multi-chromatography. J High Resolut Chromatogr Comrnun 10(5):240-243.

8. REFERENCES

*Kaplan DL, Walsh JT, Kaplan AM. 1982. Gas chromatographic analysis of glycols to determine biodegradability. Environ Sci Technol 16:723-725.

*Karlson-Stiber C, Persson H. 1992. Ethylene glycol poisoning: Experiences from an epidemic in Sweden. Clinical Toxicology 30(4):565-574.

*Kashtock M, Breder CV. 1980. Migration of ethylene glycol from polyethylene terephthalate bottles into 3% acetic acid. J Assoc Off Anal Chem 63(2):168-172.

Katz M. 1975. Intersociety committee (ISC) methods of air sampling and analysis. Health Lab Sci 12:359-422.

*Kavlock RJ, Short RD, Chemoff N. 1987. Further evaluation of an in vivo teratology screen. Teratogenesis, Carcinogenesis, and Mutagenesis 7:7-16.

*Kelner MJ, Bailey DN. 1985. Propylene glycol as a cause of lactic acidosis. Journal of Analytical Toxicology 9(1):40-42.

Kersters K, Deley J. 1963. The oxidation of glycols by acetic acid bacteria. Biochim Biophys Acta 71:311-331.

*Kersting EJ, Nielsen SW. 1965. Ethylene glycol poisoning in small animals. J Amer Vet Med Assoc 146(2):113-118.

*Khan SR, Shevock PN, Hackett RL. 1993. Magnesium oxide administration and prevention of calcium oxalate nephorolithiasis. J Urol 149:412-416.

*K.hera KS. 1991. Chemically induced alterations in maternal homeostasis and histology of conceptus: Their etiologic significance in rat fetal anomalies. Teratology 44(3):259-297.

*Khoury GA, Adbelghani AA, Anderson AC. 1993. Bioaccumulation and depuration of ethylene glycol by crayfish (Procambarus spp.) Environmental Toxicology and Water Quality 8:25-31.

Kiba N, Goto K, Furusawa M. 1986. Determination of glycerol, propane-1,2-diol and triglycerides by high-performance liquid chromatography and a post-column reactor containing immobilized glycerol dehydrogenase. Anal Chim Acta 185:287-294.

*Kirmunen T, Hannuksela M. 1989. Skin reactions to hexylene glycol. Contact Dermatitis 21(3):154-158.

*Kirk-Othmer Encyclopedia of Chemical Technology. 1978. 3rd edition. Vol. 3 , 79-95,

*Kirk-Othmer Encyclopedia of Chemical Technology. 1980. 3rd edition. Vol. 11, 933-956.

*Klaus R, Fischer W. 1987. A means of analyzing glycols especially ethylene glycol and diethylene glycol by a method used for the determination of carbohydrates in alcoholic beverages. Chromatographia 23(2):137-140.

8. REFERENCES

*Klecka GM, Carpenter CL, Landenberger BD. 1993. Biodegradation of aircraft deicing fluids in soil at low temperatures. Ecotoxicology and Environmental Safety 25:280-295.

*Konradova V, Vavrova V, Janota J. 1978. Effect of the inhalation of a surface tension-reducing substance (propylene glycol) on the ultrastructure of the epithelium of the' respiratory passages in rabbits. Folia Morpho1 26(1):28-34.

Kramer JW, Bistline D, Sheridan P, et al. 1984. Identification of hippuric acid crystals in the urine of ethylene glycol-intoxicated dogs and cats. J Am Vet Med Assoc 184(5):584.

*Kring EV, Damrell DJ, Basilio AN Jr, et al. 1984. Laboratory validation and field verification of a new passive air monitoring badge for sampling ethylene oxide in air. Am Ind Hyg Assoc J 45(10):697-707.

*Kukielka E, Cederbaum AI. 1991. Oxidation of ethylene glycol to formaldehyde by rat liver microsomes: Role of cytochrome P-450 and reactive oxygen species. Drug Metabolism and Disposition 19:1108-l 115.

*Kulick MI, Wong R, Okarma TB et al. 1985. Prospective study of side effects associated with the use of silver sulfadiazine in severely burned patients. Ann Plast Surg 14(5):407-419.

Lahti A. 1980. Nonimmunologic contact urticaria. Acta Dermato-Vemereol 60(Supp 91):1-49.

*Lamb JC, Maronpot RR, Gulati DK, et al. 1985. Reproductive and developmental toxicity of ethylene glycol in the mouse. Toxicol Appl Pharmacol 81:100-112.

*Lang RF. 1986. Determination of polar organic solutes in methanol using hot on-column injection capillary gas chromatography. Anal Chem 58(6): 1259-1261.

Lauwerys R, Bernard A, Viau C, et al. 1985. Kidney disorders and hematotoxicity from organic solvent exposure. Stand J Work Environ Health 11(Supp1 1):83-90.

*LDOTD. 1990. Fate of ethylene glycol in the environment. Baton Rouge, LA: Louisiana Department of Transportation and Development, Louisiana Transportation Research Center.

LeGatt DF, Tisdell RH. 1990. Ethylene glycol quantification: Avoid propylene glycol as an internal standard. Clin Chem 36(10):1860-1861.

Lenk W, Loehr D, Sonnenbichler J. 1989. Pharmacokinetics and biotransformation of diethylene glycol and ethylene glycol in the rat. Xenobiotic 19(9):961-979.

*Lewis RJ. 1993a. Hawley's Condensed Dictionary, 12th Edition; p 487, ethylene glycol. Van Nostrand Reinhold Co., New York.

*Lewis RJ. 1993b. Hawley's Condensed Dictionary, 12th Edition; p 970-971, propylene glycol. Van Nostrand Reinhold Co., New York.

Litovitz T. 1986. The alcohols: Ethanol, methanol, isopropanol, ethylene glycol. Pediatr Clin North Am 33(2):31 l-323.

8. REFERENCES

*Litovitz TL, Schmitz BF, Bailey KM. 1990. 1989 Annual report of the American Association of Poison Control Centers national data collection system. Toxicology 8(5):394-43 1.

*Litovitz TL, Schmitz BF, Bailey KM. 1991. 1990 Annual report of the American Poison Control Centers national data collection system. Toxicology 9(5):461-500.

*Loden M. 1986. The in vitro permeability of human skin to benxene, ethylene glycol, formaldehyde, and n-hexane. Acta Pharmacol Toxicol 58(5):382-389.

*Lokke H. 1984. Leaching of ethylene glycol and ethanol in subsoils. Water Air Soil Pollut 22:373-387.

*Lolin Y, Francis DA, Flanagan RJ, et al. 1988. Cerebral depression due to propylene glycol in a patient with chronic epilepsy the value of the plasma osmolal gap in diagnosis. Postgrad Med J 64(754):610-613.

*Louekari K, Scott AO, Salminen S. 1990. Estimation of food additive intakes. In: Branen AL, Davidson P, Salminen S, eds. Food Science Technology. Vol. 35: Food additives. New York, NY: Marcel Dekker, Inc., 9-32.

Lundberg P, Lof A, Johanson G, et al. 1991. New Swedish occupational standards for some organic solvents. Am J Ind Med 19(5):559-567.

*Lyman WJ, Reehl WF, Rosenblatt DH. 1982. Handbook of chemical property estimation methods. New York, NY: McGraw-Hill, 5 - 4.

Magerl H, Poelmann E, Hager W. 1983. Determination of ethylene glycol by head-space gas chromatography. Z Rechtsmed 90(3):205-209.

*Mallya KB, Mendis T, Guberman A. 1986. Bilateral facial paralysis following ethylene glycol ingestion. Can J Neural Sci 13(4):340-341.

Malrnlund HO, Berg A, Karlman G, et al. 1991. Considerations for the treatment of ethylene glycol poisoning based on analysis of two cases. J Toxicol Clin Toxicol 29(2):231-240.

*Manius GJ. 1979. Determination of ethylene oxide, ethylene chlorohydrin, and ethylene glycol residues in ophthalmic solutions at proposed concentration limits. J Pharm Sci 68(12): 1547-1549.

Mantica E, Botta D, Pirri L. 1986. Pollution conditions of the aquifer beneath a plant producing alkyd resins. In: Comm Eur Communities, Eur 10388. Org Micropollut Aquat Environ, 89-106.

Marion CV, Malaney GW. 1963. The oxidation of aliphatic compounds by Alcaligenes faecalis. J Water Pollut Control Fed 35:1269-1284.

*Maronpot RR, Zelenak JP, Weaver EV, et al. 1983. Teratogenicity study of ethylene glycol in rats. Drug and Chemical Toxicology 6(6):579-594.

*Marr MC, Price CJ, Myers CB, et al. 1992. Developmental stages of the CD (Sprague-Dawley) rat skeleton after maternal exposure to ethylene glycol. Teratology 46(2): 169- 18 1.

8. REFERENCES

Marshall DA, Doty RL. 1990. Taste responses of dogs to ethylene glycol, propylene glycol, and ethylene glycol-based antifreeze. J Am Vet Med Assoc 197(12): 1599-1602.

Marshall TC. 1979. Pharmacokinetics of ethylene glycol following intravenous administration to rats. Annual Report on Inhalation Toxicological Research Institute, Lovelace Biomedical Environmental Research Institute, 57 l-574.

*Marshall TC. 1982. Dose-dependent disposition of ethylene glycol in the rat after intravenous administration. J Toxicol Environ Health 10:397-409.

Marshall TC, Cheng YS. 1983. Deposition and fate of inhaled ethylene glycol vapor and condensation aerosol in the rat. Fundam Appl Toxicol 3(3):175-181.

*Martis L, Kroes T, Darby TD, et al. 1982. Disposition kinetics of ethylene oxide, ethylene glycol, and 2-chlorethanol in the dog. J Toxicol Environ Health 10:847-856.

Matsui S, Murakami T, Sasaki T, et al. 1975. Activated sludge degradability of organic substances in the waste water of the Kashima petroleum and petrochemical industrial complex in Japan. Prog Water Technol 7(3-4):645-650.

*Matusik JE, Eilers PP, Waldron EM, et al. 1993. Confirmation of identities of propylene and ethylene glycols in anchovies by tandem mass spectrometry. J Association of Official Analytical Chemistry International 76: 1344-1347.

Maurer H, Kessler C. 1988. Identification and quantification of ethylene glycol and diethylene glycol in plasma using gas chromatography-mass spectrometry. Arch Toxicol 62(1):66-69.

Maylin GA. 1980. A simple method for detecting ethylene glycol in urine by thin layer chromatography. Cornell Vet 70(2):202-205.

McCallum NK, Muirhead JM. 1982. Gas-chromatographic determination of propane-1,2-diol in flavour bases, flavoured and natural wines. Food Technology in New Zealand 17(8):34-35.

*McCann J, Choi E, Yamasaki E, et al. 1975. Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. Proc Nat Acad Sci 72:5135-5139.

*McCarroll NE, Piper CE, Keech BH. 198 1. An E. coli micro-suspension assay for the detection of DNA damage induced by direct-acting agents and promutagens. Environ Mutagen 3:429-444.

McCurdy HH, Solomons ET. 1982. Improved procedure for determination of ethylene glycol in blood. J Anal Toxicol 6(5):253-254.

McDonald TO, Kasten K, Hervey R, et al. 1973. Acute ocular toxicity of ethylene oxide, ethylene glycol, and ethylene chlorohydrin. Bull Pat-enter Drug Assoc 27(4):153-164.

*McGahey C, Bouwer EJ. 1992. Biodegradation of ethylene glycol in simulated subsurface environments. Water Science Technology 26:41-49.

8. REFERENCES

*Means JL, Anderson SJ. 198 1. Comparison of five different methods for measuring biodegradability in aqueous environments. Water Air and Soil Poll 16:301-315.

*Melnick RL. 1984. Toxicities of ethylene glycol and ethylene glycol mot-methyl ether in Fischer 344/N rats and B6C3Fl mice. Environ Health Perspect 57:147-155.

Meola JM, Rosano TG, Swift TA. 1980. Fluorimetry of ethylene glycol in serum. Clin Chem 26(12):1709.

*Merck Index. 1989a. The Merck index: An encyclopedia of chemicals, drugs, and biologicals. 11th ed. Budavari S, ed. Rahway, NJ: Merck and Co., Inc., 379, 7810

*Merck Index. 1989b. The Merck index: An encyclopedia of chemicals, drugs, and biologicals. 11th ed. Budavari S, ed. Rahway, NJ: Merck and Co., Inc., 3759, 7810.

Mikheev MI, Gorlinskaya Y, Solovyova TV. 1990. The body distribution and biological action of xenobiotics. J Hyg Epidemiol Microbial Immunol 34(4):329-336.

Mill T, Hendry DG, Richardson H. 1980. Free radical oxidants in natural waters. Science 207(22):886-887.

*Miller ON, Bazzano G. 1965. Propanediol metabolism and its relation to lactic acid metabolism. Ann NY Acad Sci 119:959-973.

Miller W. 1990. Ethylene glycol toxicity. Del Med J 62(10):1267-1272.

Mitsuhashi Y, Hamano T, Tanaka K, et al. 1985. [Enzymatic analysis of propylene glycol in foods by the use of glycerol dehydrogenase.] J Food Hyg Sot Jpn 26:290-294. (Japanese)

Moffatt EJ, Hagardom AN, Ferslew KE. 1986. A gas-liquid chromatographic method for quantitation of 1,3-butylene glycol in whole blood or plasma and the separation of the short chain glycols. J Anal Toxicol 10(1):35-37.

Momont SL, Dahlberg PJ. 1989. Ethylene glycol poisoning. Wis Med J 88(9):16-20.

Moriarty RW, McDonald RH Jr. 1974. The spectrum of ethylene glycol poisoning. Clin Toxicol 7(6):538-596.

*Morris HJ, Nelson AA, Calvery HO. 1942. Observations on the chronic toxicities of propylene glycol, ethylene glycol, diethylene glycol, ethylene glycol mono-ethyl-ether and diethylene glycol mono-ethyl-ether. J Pharmacol Exp Therap 74:266-273.

*Morshed KM, Desjeux JF, Nagpaul JP, et al. 1991a. The effect of propanediols on the intestinal uptake of nutrients and brush boder membrane enzymes in the rat. Biochem Med Metab Biol 45(2):161-170.

*Morshed KM, Helgoualch AL, Nagpaul JP, et al. 1991b. The role of propylene glycol metabolism in lactatemia in the rabbit. Biochemical Medicine and Metabolic Biology 46:145-151.

8. REFERENCES

*Morshed KM, Jain SK, McMartin K. 1993. Acute toxicity of propylene glycol: An assessement using cultured proximal tuble cells of human origin. Funda App Toxicol 23:38-43.

Morshed KM, Nagpaul JP, Amma MKP, et al. 1991. The role of propylene glycol metabolism in lactatemia in the rabbit. Biochem Med Metab Biol 46:145-151.

*Morshed KM, Nagpaul JP, Majumdar S, et al. 1988. Kinetics of propylene glycol elimination and metabolism in rat. Biochem Med Metab Biol 39(1):90-97.

*Morshed KM, Nagpaul JP, Majumdar S, et al. 1989. Kinetics of oral propylene glycol-induced acute hyperlactatemia. Biochem Med Metab Biol 42(2):87-94.

Murphy MJ, Ray AC, Jones LP, et al. 1984. 1,3-Butanediol treatment of ethylene glycol toxicosis in dogs. Am J Vet Res 45(11):2293-2295.

*Mushtaq E, Green LE. 1989. Effect of ethylene glycol on the interaction of different myosin subfragment l-Nucleotide complexes with actin. Biochemistry 2864786482.

*Muzeni RJ. 1985. Rapid gas chromatographic determination of ethylene oxide, ethylene chlorohydrin, and ethylene glycol residues in rubber catheters. J Assoc Off Anal Chem 68(3):506-508.

Myers VS Jr, Usenik EA. 1969. Propylene glycol intoxication of horses. J Am Vet Med Assoc 155(12):1841.

*Nagano K, Nakay ama E, Oobayashi H, et al. 1984. Experimental studies on toxicity of ethylene glycol alkyl ethers in Japan. Environ Health Perspect 57:75-84.

*NAS/NRC. 1989. Biologic markers in reproductive toxicology. National Academy of Sciences/National Research Council. Washington, DC: National Academy Press, 15-35.

*Nater JP, Baar AJM, Hoedemaeker J. 1977. Histological aspects of skin reactions to propylene glycol. Contact Dermatitis 3:181-185.

*NATICH. 199 1. National Air Toxics Information ClearingHouse. Data base report on state, local, and EPA air toxics activities. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Washington, DC. August 13, 1991.

*Needham LL, Hill RH Jr, Otti DL, et al. 1982. Electron-capture, capillary column gas chromatographic determination of low-molecular-weight diols in serum. J Chromatogr 233:9-17.

*Neeper-Bradley TL. 1990. Developmental toxicity evaluation of ethylene glycol administered by gavage to CD (Sprague-Dawley) rats: Determination of a Bno observed effect level (NOEL). Bushy Run Research Center. CMA Project Report 52-656.

Nelson EB, Egan JM, Abemethy DR. 1987. The effect of propylene glycol on antipyrine clearance in humans. Clin Pharmacol Ther 41(5):571-573.

Nestrick TJ, Lamparski LL, Peters TL. 1983. Low-splitting-rating injector for capillary gas chromatography. Anal Chem 55(12):2009-2011.

8. REFERENCES

*NFPA. 1994a. Fire Protection Guide to Hazardous Materials, 11 th Edition, page 325-50; ethylene glycol National Fire Protection Association, Quincy, MA.

*NFPA. 1994b. Fire Protection Guide to Hazardous Materials, 11 th Edition, page 325-82, propylene glycol National Fire Protection Association, Quincy, MA.

Nguyen TD, Matsuura T, Sourirajan S. 1987. A fundamental approach to reverse-osmosis concentration and fractionation of organic chemicals in aqueous solutions for environmental analysis. In: Suffet IH, Malaiyandi M, eds. Advances in chemistry series, 214. Organic pollutants in water: Sampling, analysis, and toxicity testing. Washington, DC: American Chemical Society, 139-162.

NIOSH. 1974. National Occupational Hazard Survey (NOHS). Volume 1: Survey manual. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Office of Occupational Health Surveillance and Biometrics.

*NIOSH. 1984. NIOSH manual of analytical methods. 3rd ed. Washington, DC: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. NIOSH100184336.

*NIOSH. 1990. National Occupational Exposure Survey (NOES) 1981-1983. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

*NIOSH. 1994. Health hazard evaluation report. National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Public Health Service, U. S. Department of Health and Human Services. Heta 90-0355-2449.

*NRC. 1994. Personal conversation with K. Bakshi to Marion Deerhake, Research Triangle Institute, regarding the compilation of current EEGLs and CEGLs. National Research Council, Committee on Toxicology, National Academy of Sciences.

*NREPC. 1986. New or modified sources emitting toxic air pollutants. Frankfort, KY: Department for Environmental Protection, National Resources and Environmental Protection Cabinet. 401 KAR 63:022.

*NTDB. 1995. (CD-ROM) US Dept. of Commerce Census, Economics and Statistics Administration. Washington DC

*NTP. 1985. Propylene glycol: Reproduction and fertility assessment in CD-l mice when administered in drinking water. Final report. National Toxicology Program. NTP-84-FACB-038.

*NTP. 1988. Developmental toxicity evaluation of ethylene glycol (CAS No. 107-21-1) in CD rats. Final report. National Toxicology Program, National Institute of Environmental Health Sciences. NTP-88-079.

*NTP. 1992. Toxicology and carcinogenesis studies of ethylene glycol in B6C3Fl mice. Document no. NTP TR 413. Washington, DC: U.S. Deparment of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program. NTH publication no. 91-3144.

8. REFERENCES

*Ochs ML, Glick MR, Ryder WW, et al. 1988. Improved method for emergency screening for ethylene glycol in serum. Clin Chem 34(7):1507-1508.

*OHM/TADS. 1985. Oil and Hazardous Materials/Technical Assistance Data System, Chemical Information Systems, Inc., Baltimore, MD. December, 1985.

Oliver JJ. 1993. A comatose man with marked acidosis and crystaluria. Hospital Practice 28(7):86-88.

*OSHA. 1987. Access to employee exposure and medical records. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.20.

*OSHA. 1988. Access to employee exposure and medical records. Occupational Safety and Health Administration. Federal Register 53:38140, 38163.

OSHA. 1989a. Toxic and hazardous substances. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000

OSHA. 1989b. Toxic and hazardous substances. Occupational Safety and Health Administration. Federal Register 54:2920-2960.

*OTA. 1990. Neurotoxicity: Identifying and controlling poisons of the nervous system. Office of Technology Assessment, Washington, DC. OTA-BA-438.

*Ouattara AS, Cuzin N, Traore AS, et al. 1992. Anaerobic degradation of 1,2-propanediol by a new Desulfovibrio strain and D. alcoholovorans. Arch Microbial 158:218-22s.

*O&ebo S, Jacobsen D, Sejersted OM. 1987. Determination of ionic metabolites from ethylene glycol in human blood by isotachophoresis. J Chromatogr Biomed Appl 416(1): 111-118.

Pant SK, Thomas KM, Gupta PN, et al. 1989. Detection of presence of dietbylene glycol in glycerin. Indian J Pharm Sci 51(2):57-58.

*Parry MF, Wallach R. 1974. Ethylene glycol poisoning. Amer J Med 57(1):143-150.

Pearl RG, Rice SA. 1989. Propylene-glycol-induced pulmonary hypertension in sheep. Pharmacology 39(6):383-389.

*Penumarthy L, Oehme FW. 1975. Treatment of ethylene glycol toxicosis in cats. Am J Vet Res 36(2):209-212.

Per1 W, Silverman F, Delea AC, et al. 1976. Permeability of dog lung endothelium to sodium, diols, amides, and water. Am J Physiol 230(6):1708-1721.

*Peterson CD, Collins AJ, Himes JM, et al. 1981. Ethylene glycol poisoning: Pharmacokinetics during therapy with ethanol and hemodialysis. New Eng J Med 304:21-23.

Peterson RL, Rodgerson DO. 1974. Gas-chromatographic determination of ethylene glycol in serum. Clin Chem 20(7):820-824.

8. REFERENCES

*Petroff OA, Yu RK, Ogino T. 1986. High-resolution proton magnetic resonance analysis of human cerebrospinal fluid. J Neurochem 47(4): 1270- 1276.

*Pfeiffer EH, Dunkelberg H. 1980. Mutagenicity of ethylene oxide and propylene oxide and of the glycols and halohydrins formed from them during the fumigation of foodstuffs. Food Cosmet Toxicol 18:115-118.

Poikolainen K, Vuori E. 1985. Risk of fatal alcohol poisoning by marital and occupational status. Alcohol Alcohol 20(3):329-332.

*Price CJ, Kimmell CA, Tyl RW, et al. 1985. The developmental toxicity of ethylene glycol in rats and mice. Toxicol Appl Pharmacol 81(1):113-127.

Price KS, Waggy GT, Conway RA. 1974. Brine shrimp bioassay and seawater BOD of petrochemicals. J Water Pollut Contr Fed 46(1):63-77.

Quince JR, Gardner GL. 1982. Recovery and treatment of contaminated groundwater: Part II. Ground Water Monitoring Review, Special Issue. Fall 1982:6-13.

Quinn DA, Robinson D, Hales CA. 1990. Intravenous injection of propylene glycol causes pulmonary hypertension in sheep. J Appl Physiol 68(4):1415-1420.

*Raja LMV, Elamvaluthy G, Palaniappan R, et al. 1991. Novel biotreatment process for glycol waters. Appl Biochem Biotechnology (28-29):827-842.

Rajagopal G, Ramakrishnan S. 1975. A new method for estimation of ethylene glycol in biological material. Anal Biochem 65(1-2):132-136.

Rajagopal G, Ramakrishnan S. 1978. Effect of ethylene glycol toxicity on hepatic carbohydrate metabolism in rats. Toxicol Appl Pharmacol 46(2):507-516.

*Rajagopal G, Venkatesan K, Ranganathan P, et al. 1977. Calcium and phosphorus metabolism in ethylene glycol toxicity in rats. Toxicol Appl Pharmacol 39(3):543-547.

*Randall PM, Gavaskar AR. 1993. Evaluation of filtration and distillation methods for recycling automotive coolants. U.S. Environmental Protection Agency, Risk Reduction Engineering Laboratory, Office of Research and Development, Cincinnati, OH. EPA/600/J-931435. PB 94-101912

*Rice SF, Steeper RR, LaJeunesse CA. 1993. Destruction of representative navy wastes using supercritical water oxidation. Sandia National Laboratories, Albuquerque, NM. DE 94-003139

*Richardson KE. 1973. The effect of partial hepatectomy on the toxicity of ethylene glycol, glycolic acid, glyoxilic acid and glycine. Toxicol Appl Pharamacol 24:530-538.

*Riggs PC, Barry BW. 1990. Shed snake skin and hairless mouse skin as model membranes for human skin during permeation studies. J Invest Dex-matol 94(2):235-240.

*Riley JH, Stahr HM, O'Brien S, et al. 1982. Urine and tissue oxalate and hippurate levels in ethylene glycol intoxication in the dog. Veterinary Hum Toxicol 24(5):331-334.

8. REFERENCES

*Roberts JA, Seibold HR. 1969. Ethylene glycol toxicity in the monkey. Toxicol Appl Pharmacol 15(3):624-631.

*Robertson OH, Loosli CG, Puck TT. 1947. Test for chronic toxicity of propylene glycol and triethylene glycol on monkeys and rats by vapor inhalation and oral administration. J Pharmacol Exper Therap 91:52-76.

*Robinson D, McCoy CA. 1989. Ethylene glycol toxicity. Crit Care Nurse 9(6):70-74.

Robinson DW, Reive DS. 1981. A gas chromatographic procedure for quantitation of ethylene glycol in postmortem blood. J Anal Toxicol 5(2):69-72.

Robinson M, Pond CL, Laurie RD, et al. 1990. Subacute and subchronic toxicity of ethylene glycol administered in drinking water to Sprague-Dawley rats. Drug Chem Toxicol 13:43-70.

*Rofe AM, Bais R, Conyers RAJ. 1986. The effect of dietary refined sugars and sugar alcohols on renal calcium oxalate deposition in ethylene glycol-treated rats. Food Chem. Toxic 24(5):397-403.

*Romaguera C, Perez AG, Moran M, et al. 1981. Propylene glycol in standard patch tests. Contact Dermatitis. 7(6):346.

Rossa V, Weber U. 1990. Effect of ethylene glycol on rabbit retinas. Ophthalmologica 200(2):98-103.

*Ross01 M. 1990. Theatrical fogs and smokes: A report on their hazards. American Guild of Musical Artists.

*Ross01 M. 1993. Comments on Technical Report for Ethylene GlycoVPropylene Glycol. Submitted to ATSDR on Sept. 7, 1993.

*Rothman A, Normann SA, Manoguerra AS, et al. 1986. Short-term hemodialysis in childhood ethylene glycol poisoning. J Pediatr 108:153-155.

*Rowe VK, Wolf MA. 1982. Glycols. In: Clayton GD, Clayton FE, eds. Patty's industrial hygiene and toxicology. Volume 2C: Toxicology. 3rd. ed. New York, NY: John Wiley & Sons, 3817-3853.

Rowland J. 1987. Incidence of ethylene glycol intoxication in dogs and cats seen at Colorado State University Veterinary Teaching Hospital. Vet Hum Toxicol 29(1):41-44.

*Ruddick JA. 1972. Toxicology, metabolism, and biochemistry of 1,2-propanediol. Toxicol Appl Pharmacol 21(1):102-111.

Ruegsegger GJ, Schultz LH. 1986. Use of a combination of propylene glycol and niacin for subclinical ketosis. J Dairy Sci 69(5):1411-1415.

*Ryder KW, Glick MR, Jackson SA. 1986. Emergency screening for ethylene glycol in serum. Clin Chem 32(8):1574-1577.

8. REFERENCES

*Saini M, Meenakshi KM, Amma MKP. 1987. Propane 1,2 diol induced changes in plasma proteins and enzymes on acute oral ingestions in female rats. Res Bull Panjab Univ Sci 38(3):79-86,

*Sakoda T, Horiuti K. 1992. Effects of ethylene glycol and calcium on the kinetics of contration induced by photo-released of low concentrations of ATP in rat psoas muscle fibres. J Muscle Res Cell Motil 13(4):464-472.

Saladino R, Shannon M. 1991. Accidental and intentional poisonings with ethylene glycol in infancy: Diagnostic clues and management. Pediatr Emerg Care 7(2):93-96.

Schramm M, Wanick AW, Fuller WH. 1986. Permeability of soils to four organic liquids and water. Hazardous Waste and Hazardous Materials 3(1):21-27.

*Schuler RL, Hardin BD, Niemeier RW, et.al. 1984. Results of testing fifteen glycol ethers in a short-term in vivo reproductive toxicity assay. Environmental Health Perspectives 57: 141-146.

*Schumacher JN, Green CR, Best FW, et al. 1977. Smoke composition: An extensive investigation of the water-soluble portion of cigarette smoke. J Agric Food Chem 25(2):310-320.

Sheldon LS, Hites RA. 1979. Environmental occurrence and mass spectral identification of ethylene glycol derivatives. Sci Total Environ 11(3):279-286.

Sherertz EF, Sloan KB, McTieman RG. 1990. Transdermal delivery of 5-fluorouracil through skin of hairless mice and humans in vitro: A comparison of the effect of formulations and a prodrug. Arch Dermatol Res 282(7):463-468.

*Shoemaker JD, Lynch RE, Hoffmann JW, et al. 1992. Misidentification of propionic acid as ethylene glycol in a patient with methylmalonic acidemia. J Pediatr 120:417-421.

*Siew S, Matta RK, Johnson M. 1975a. Investigation of “crystallosis” in ethylene glycol toxicity. Scanning Electron Microscopy 8:555-562.

*Siew S, Matta RK, Johnson M. 1975b. Microanalysis of crystals in biological tissue. In: Proceedings from the 10th Annual Conference of the Microbeam Analysis Society, MGM Hotel, Las Vegas, Nevada., August 11-15, 1975. Bethlehem, PA: Lehigh University, Metallurgy and Materials Science Department, 48-A - 48-D.

*Sills RD, Blakeslee PA. 1992. The environmental impact of deicers in airport stormwater runoff. In: Chemical Deicers and the Environment. Boca Raton, FL: Lewis Publishers, 323-340.

*Simmons P, Branson D, Bailey R. 1976. 1,2,4-Trichlorobenzene: Biodegradable or not? In: Book pap, Int Tech Conf. Research Triangle Park, NC: American Association Text, 212-217,

Simpson E. 1985. Some aspects of calcium metabolism in a fatal case of ethylene glycol poisoning. Ann Clin Biochem 2290-93.

*Sisfontes L, Nyborg G, Jones AW, et al. 1986. Occurrence of short chain aliphatic diols in human blood: Identification by gas chromatography-mass spectrometry. Clin Chim Acta 155(2):117-122.

8. REFERENCES

Slave T, Mihail A, Burmaz N. 1974. [Degradation of some organic impurities in residual waters.] Rev Chim 25:666-670. (Hungarian)

Smith BJ, Anderson BG, Smith SA, et al. 1990. Early effects of ethylene glycol on the ultrastmcture of the renal cortex in dogs. Am J Vet Res 51(1):89-96.

*Smith NB. 1984. Determination of serum ethylene glycol by capillary gas chromatography. Clin Chim Acta 144(2-3):269-272.

Smith NB. 1987a. Identification and elimination of an ethylene glycol determination artifact. Clin Chim Acta 162(1):105-108.

Smith NB. 1987b. Measurement of ethylene glycol in biological specimens. Ann Clin Biochem 24:639-640.

Smith NB, Rawal N. 1987. Lack of interference of tris(hydroxymethyl)methylarnine with the determination of volatile alcohols or ethanediol in serum by capillary gas chromatography. Clin Chem 33(12):2324.

Speece RE. 1983. Anaerobic biotechnology for industrial wastewater treatment. Environ Sci Technol 17(9):416A-427A.

Speth PA, Vree TB, Neilen NP, et al. 1987. Propylene glycol pharmacokinetics and effects after intravenous infusion in humans. Ther Drug Monit 9(3):255-258. .

*Spillane L, Roberts JR, Meyer AE. 1991. Multiple cranial nerve deficits after ethylene glycol poisoning. Ann Emerg Med 20(2):208-210.

*Spitz HD, Weinberger J. 197 1. Determination of ethylene oxide, ethylene chlorohydrin, and ethylene glycol by gas chromatography. J Pharm Sci 60(2):271-274.

*SRI. 1989. Directory of Chemical Producers -United States of America. Stanford Research Institute International Menlo Park, Ca.

*SRI. 1991. Directory of Chemical Producers -United States of America. Stanford Research Institute International Menlo Park, Ca. 620-621; 936

*SRI. 1993. Directory of Chemical Producers -United States of America. Stanford Research Institute International Menlo Park, Ca. 598; 890

*SRI. 1995. Directory of Chemical Producers -United States of America. Stanford Research Institute International Menlo Park, Ca. 590; 875

Stein ZLG, Bar-kin RL, Lipscomb JW, et al. 1983. Ethylene glycol toxicity and treatment. Drug Intel1 Clin Pharm 17:376-377.

Steinhart B. 1990. Case report: Severe ethylene glycol intoxication with normal osmolal gap-“a chilling thought.” J Emerg Med 8(5):583-585.

8. REFERENCES

Steinke W, Arendt G, Mull M, et al. 1989. Good recovery after sublethal ethylene glycol intoxication: Serial EEG and CT findings. J Neurol 236(3):170-173.

*Stenback F, Shubik P. 1974. Lack of toxicity and carcinogenicity of some commonly used cutaneous agents. Toxicol Appl Pharmacol 30:7-13.

Stevens HM. 1986. The detection of some non-drug poisons in simulated stomach contents by diffusion into various color reagents. J Forensic Sci 26:(2)137-145.

Studer VA, Grummer RR, Bertics SJ, et al. 1993. Effect of prepartum propylene glycol administration'on periparturient fatty liver in dairy cows. J Dairy Sci 76(10):2931-2939.

*Suber RL, Deskin R, Nikiforov I, et al. 1989. Subchronic nose-only inhalation study of propylene glycol in Sprague-Dawley rats. Food Chem Toxicol 27(9):573-584.

*Swarm RL, Laskowaski DA, McCall PJ, et al. 1983. A rapid method for the estimation of the environmental parameters octanol water partition coefficient, soii sorption constant, water to air ratio, and water solubility. Dow Chemical Company, Springer-Verlag New York Inc. Residue Reviews 85: 18-28.

*Swenberg JA, Petzold GL, Harbach PR. 1976. In vitro DNA damage/alkaline elution assay for predicting carcinogenic potential. Biochemical and Biophysical Research Communications 72(2):732-738.

*Takeuchi Y, Yasukawa H, Yamaoka Y, et al. 1993. Effects of Oleic Acid/propylene glycol on rat abdominal stratum corneum: Lipid extraction and appearance of propylene glycol in the dermis measured by fourier tranforrn infrared/attenuated total reflectance (FT-IR/ATR) spectroscopy. Chem Pharm. Bull 41(8):1434-1437.

*Takeuchi Y, Yasukawa H, Yamaoka Y, et al. 1995. Behavior of Propylene Gycol (PG) in dermis after treatment of rat intact skin surface with fatty acids, fatty amines or azone dissolve in PG. Biol Pharm Bull 18(2):304-309.

Tarr BD, Winters LJ, Moore MP, et al. 1985. Low-dose ethanol in the treatment of ethylene glycol poisoning. J Vet Pharmacol Ther 8(3):254-262.

*Texas. 1994. Personal conversation with M. Aponte-Pons to Marion Deerhake, Research Triangle Institute, regarding screening levels. Texas Conservation Commission (7/19/94).

Thrall MA, Grauer GF, Mero KN. 1984. Clinicopathologic findings in dogs and cats with ethylene glycol intoxication. J Am Vet Med Asso 184(1):37-41.

*Trancik RJ, Maiback HI. 1982. Propylene glycol irritation or sensitization? Contact Dermatitis, 8:185-189.

*TRI90. 1992. Toxic Chemical Release Inventory. National Library of Medicine, National Toxicolgy Information Program, Bethesda, MD.

8. REFERENCES

*TRI91. 1993. Toxic Chemical Release Inventory. National Library of Medicine, National Toxicolgy Information Program, Bethesda, MD.

*TRI92. 1994. Toxic Chemical Release Inventory. National Library of Medicine, National Toxicolgy Information Program, Bethesda, MD.

*TRI93. 1995. Toxic Chemical Release Inventory. National Library of Medicine, National Toxicolgy Information Program, Bethesda, MD.

*Triosi FM. 1950. Chronic intoxication by ethylene glycol vapour. Brit J Industr Med 7:65-69.

Tsukamura M. 1966. Utilization of glycols and certain other carbohydrates by mycobacteria as sole carbon sources. Amer Rev Resp Dis 94:796-798.

*Tucker SP, Deye GJ. 1981. Sampling and analytical method for ethylene glycol in air. Anal Lett 14(A12):959-976.

Turpeinen M. 1991. Absorption of hydrocortisone from the skin reservoir in atopic dermatitis. Br J Dermatol 124(4):358-360.

*Tyl RW. 1985. Evaluation of the teratogenic potential of ethylene glycol aerosol in the CD rat and CD-l mouse. Bushy Run Research Center, Union Carbide Corp., Report No. 48-100.

*TY1 RW. 1988a. Ethylene glycol: Developmental toxicity evaluation of the aerosol in CD-l mice by nose-only or whole-body exposure. Bushy Run Research Center, Union Carbide Corp., Report No. 50-121.

*Tyl RW. 1988b. Developmental toxicity evaluation of ethylene glycol applied cutaneously to CD-l mouse. Bushy Run Research Center. CMA Project Report 50-597.

*Tyl RW. 1989. Developmental toxicity evaluation of ethylene glycol administrated by gavage to CD-l mice: Determination of a “no-observed-effect-level” (NOEL). Bushy Run Research Center, CMA Project Report 51-591.

*Tyl RW, Price CJ, Mar-r MC, et al. 1993. Developmental toxicity evaluation of ethylene glycol by gavage in New Zealand White (NZW) rabbits. Fundamental and Applied Toxicology 20:402-412.

*Underwood F, Bennett WM. 1973. Ethylene glycol intoxication: Prevention of renal failure by aggressive management. J Am Med Asso 226(12):1453-1454.

*Vale JA. 1979. Ethylene glycol poisoning. Vet Hum Toxicol 21: 118-120.

Van Rillaer WG, Beemaert H. 1983. Determination of residual propane-Zdiol and propane-1,2-diol in soft drinks by glass-capillary gas chromatography. Z Lebensm-Unters-Forsch 177(3):196-199.

Van Stee EW, Harris AM, Horton ML, et al. 1975. The treatment of ethylene glycol toxicosis with pyrazole. J Pharmacol Exp Ther 192(2):251-259.

8. REFERENCES

*VANR. 1988. Vermont Agency of Natural Resources. Department of Environmental Conservation and Groundwater Protection. Washington, DC: Bureau of Affairs.

Vassalli L, Harris DM, Gradini R, et al. 1988. Inflammatory effects of topical antibiotic suspensions containing propylene glycol in chinchilla middle ears. Am J Otolaryngol 9(1):1-S.

Vernon J, Brummett R, Walsh T. 1978. The ototoxic potential of propylene glycol in guinea-pigs. Arch Otolaryngol 104(12):726-729.

Verschueren K. 1977. Handbook of environmental data on organic chemicals. New York, NY: Van Nostrand Reinhold Company, 646-647, 1029.

*Vesper SJ, Murdoch LC, Hayes S, et al. 1994. Solid oxygen source for bioremediation in subsurface soils. J Hazardous Materials 36: 265-274.

Vincent R, Cicolelia A, Poirot P. 1990. Determination of glycol ethers in working atmospheres. Analusis 18(10):591-596.

von Sonntag C. 1984. Carbohydrate radicals: From ethylene glycol to DNA strand breakage. Int J Radiat Biol Relat Stud Phys Chem Med 46(5):507-519.

*Walker JE, Kaplan DL. 1992 . Biological degradation of explosives and chemical agents. Biodegradation 3(2-3):369-385.

*Walters KM, Mason WD, Badr MZ. 1993. Effect of propylene glycol on the disposition of dramamine in the rabbit. Drug Metabolism and Disposition 21:305-308.

*Walton EW. 1978. An epidemic of antifreeze poisoning. Med Sci Law 18(4):231-237,
*Wang F, Cassidy K, Lum B. 1993. Incineration alternatives for combustible waste. Ultraviolet/hydrogen peroxide process. Final Report to Rocky Flats Plant, Lawrence Livermore National Laboratory, CA. DE 93 018905.

*Ware GW. 1988. Ethylene Glycol. Review of Environmental Contamination and Toxicology 106:133-141.

*Warshaw TG, Herrmann F. 1952. Studies of skin reactions to propylene glycol. J Invest Dermatol 19:423-429.

Watson GK, Jones N. 1977. The biodegradation of polyethylene glycols by sewage bacteria. Water Research 11:95-100.

*Weast RC. 1988a. CRC Handbook of Chemistry and Physics, 69th Edition, entry 6680, ethanediol CRC Press, Boca Raton, FL.

*Weast RC. 1988b. CRC Handbook of Chemistry and Physics, 69th Edition, entry 11898, 1,2-propanediol CRC Press, Boca Raton, FL.

8. REFERENCES

*Weil CS, Woodside MD, Smyth HF Jr, et al. 1971. Results of feeding propylene glycol in the diet to dogs for two years. Food Cosmet Toxicol 9(4):479-490.

*Weiss DJ, Bauer MC, Murphy MJ, et al. 1992. Increased mechanical fragility and intravascular lysis of erythrocytes in cats fed a propylene glycol-containing diet. Comparative Haematology International 2:157-161.

*Weiss DJ, McClay CB, Christopher MM, et al. 1990. Effects of propylene glycol-containing diets on acetaminophen-induced methemoglobinemia in cats. J Am Vet Med Assoc 196(11):1816-1819.

*Wiener HL, Richardson KE. 1988. The metabolism and toxicity of ethylene glycol. Res Commun Subst Abus 9(2):77-87.

Wierda A, Verhoeff J, van Dijk S, et al. 1985. Effects of trenbolone acetate and propylene glycol on pregnancy toxaemia in ewes. Vet Ret 116(11):284-287.

*Willets A. 1981. Bacterial metabolism of ethylene glycol. Biochim Biophys Acta 677(2):194-199.

*Williamson SA, Iverson WG. 1993. Determination of short-chain diols and selected fermentation by-products in beer. J American Society of Brewery Chemists 51:114-118.

*Willis CM, Stephens CJ, Wilkinson JD. 1989. Epidermal damage induced by irritants in man: A light and electron microscopic study. J Invest Dermatol 93(5):695-699.

*Willis CM, Stephens CJM, Wilkinson JD. 1988. Experimentally-induced irritant contact dermatitis: Determination of optimum irritant concentrations. Contact Dermatitis 18(1):20-24.

*Wills JH, Coulston F, Harris ES, et al. 1974. Inhalation of aerosol&d ethylene glycol by man. Clin Toxicol 7(5):463-476.

Willson JE. 1970. Ethylene oxide sterilant residues. Bull Parenter Drug Assoc 24(5):226-234.

*Winek CL, Shingleton DP, Shanor SP. 1978. Ethylene and diethylene glycol toxicity. Clin Toxicol 13(2):297-324.

*Winter ML, Ellis MD, Snodgrass WR. 1990. Urine fluorescence using a Wood’s lamp to detect the antifreeze additive sodium fluorescein: A qualitative adjunctive test in suspected ethylene glycol ingestions. Ann Emer Med 19663-667.

Wittman JS III, Bawin RR. 1974. Stimulation of gluconeogenesis by propylene glycol in the fasting rat. Life Sci 15(3):515-524.

Wittman JS III, Bawin RR, Miller ON. 1975. Inhibition of propylene glycol stimulated gluconeogenesis by quinolinic acid in the fasting rat. Arch Biochem Biophys 170(1):294-299.

*Woodside MD. 1982. Ethylene glycol: Twenty-four month feeding in the diet of rats. Bushy Run Research Center, Union Carbide Chemicals and Plastics Co., Inc., Report No. 44-109.

8. REFERENCES

*Woolf AD, Wynshaw-Boris A, Rinaldo P, et al. 1992. Intentional infantile ethylene glycol poisoning presenting as an inherited metabolic disorder. Pediatrics 120(3):421-424.

Wright CG, Bird LL, Meyerhoff WL. 1991. Tympanic membrane microstructure in experimental cholesteatoma. Acta Otolaryngol 111(1):101-111.

*Wu NM, Malinin TI. 1987. High performance liquid chromatography determination of ethylene glycol and ethylene chlorohydrin in tissues. J Anal Toxicol 11(2):63-66.

Yaws CL, Yang HC, Hoppier JR, et al. 1990. Organic chemicals: Water solubility data. Chem Engineering 97:115-118.

*Yu DK, Elmquist WF, Sawchuk RJ. 1985. Pharmacokinetics of propylene glycol in humans during multiple dosing regimens. J Pharm Sci 74(8):876-879.

Yu DK, Sawchuck RJ. 1983. Gas-liquid chromatographic determination of propane-1,2-diol in plasma and urine. Clin Chem 29(12):2088-2090.

Yu DK, Sawchuk RJ. 1987. Pharmacokinetics of propylene glycol in the rabbit. J Pharmacokinetic Biopharm 15(5):453-471.

*Zeiger E, Anderson B, Haworth S, et al. 1987. Salmonella mutagenicity tests: III. Results from the testing of 255 chemicals. Environ Mutagen 9(Suppl 9):1-109.

*Zeiss J, Velasco ME, McCann KM, et al. 1989. Cerebral CT of lethal ethylene glycol intoxication with pathologic correlation. Am J Neuroradiol 10(2):440-442.

Zimina LN, Budarina LS, Nazarenko AF. 1977. Morphological changes in the liver and kidneys in ethylene glycol poisoning. Arkh Pat01 39(2):51-58.

9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological profiles.

Adsorption Coefficient (K_{oc}) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical 'in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 35.5 days or more, as specified in the Toxicological profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure-- Exposure to a chemical for a duration of 15-364 days, as specified in the toxicological profiles.

9. GLOSSARY

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In vivo -- Occurring within the living organism.

Lethal Concentration($_{L0}$) (LC_{LO}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration($_{50}$) (LC_{50}) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose($_{LO}$) (LD_{LO}) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose($_{50}$) (LD_{50}) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time($_{50}$) (LT_{50}) -- A calculated period of time within which a specific concentraGon of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level -- An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced a'this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow}) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Lit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

9. GLOSSARY

q_1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The ql* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defmed experimental an&& population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s):	Ethylene glycol
CAS number(s):	107-21-1
Date:	December 1995
Profile status:	Third Draft Post Public Comment
Route:	[X] Inhalation [ ] Oral
Duration:	[X] Acute [ ]Intermediate [ ] Chronic
Key to figure:	4
Species:	Mouse

MRL: 0.5 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Tyl 1988a

Experimental design: Timed-pregnant CD-1 mice were exposed to ethylene glycol aerosol on gestational days (Gd) 6–15, 6 hours per day by nose-only procedures at doses of 0, 500, 1,000, or 2,500 mg/m^3 (0, 197, 394, or 985 ppm) target concentration. Control animals were exposed to water aerosol (4,200 mg/m^3 or 5,705 ppm). Females were weighed, observed daily for clinical signs, and evaluated for water consumption. At sacrifice on Gd 18, females were evaluated for body weight, gravid uterine weight, and liver and kidney weight. Ovarian corpora lutea were counted and all uterine implantation sites evaluated. Maternal body weight was unaffected. No dose-related clinical signs were noted. Water consumption was not significantly affected. At sacrifice, liver weight was not affected. Absolute maternal kidney weight was increased at 394 and 985 ppm and relative maternal kidney weight was increased at 985 ppm, but no treatment related lesions were observed.

Effects noted in study and corresponding doses: A clear dose response relationship was observed for absolute and relative kidney weight:

197 ppm EG = low dose (NOAEL)
394 ppm EG = mid dose (increased absolute kidney weight; less serious LOAEL)
985 ppm EG = high dose (increased absolute and relative kidney weight)

Dose endpoint used for MRL derivation:

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: No conversion was used.

APPENDIX A

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
1) Doses in animals were converted from mg/m^3 to ppm:

500 mg/m^3 x 24.45/62.07 (mol. wt. EG) = 197 ppm; 1,000 mg/m^3 = 394 ppm;
2,500 mg/m^3 = 985 ppm

Was a conversion used from intermittent to continuous exposure?
If so, explain: Doses were converted from a 6 hours per day exposure to a continuous exposure by multiplying by 6/24:

197 ppm x 6/24 = 49.4 ppm;
394 ppm x 6/24 = 98.5 ppm;
985 ppm x 6/24 = 246.2 ppm

Other additional studies or pertinent information that lend support to this MRL: Tyl (1988) was a study designed to determine a NOAEL for inhalation by nose-only exposure. A previously conducted study (Tyl 1985), used whole body exposure, but was considered flawed due to the possibility of ingestion of ethylene glycol from the fur of exposed animals through grooming. Thus, Tyl (1988) used the most conservative exposure paradigm for inhalation studies, which lends greater credence to the assumption that the observed effects were due to inhalation of the compound, only. In this regard, metabolic acidosis and renal toxicity are the hallmarks of ethylene glycol toxicity. Both these effects arise from the metabolism of ethylene glycol to glycolic acid (acidosis) and oxalate (oxalate nephrosis). Frank renal toxicity from ethylene glycol is usually accompanied by the observation of oxalate crystals in the renal tissue and in the urine. In Tyl (1988), oxalate nephrosis was not observed. However, increased kidney weight has been observed in conjunction with oxalate nephrosis in other studies after oral exposure (DePass et al. 1986a; Woodside 1982). It may be assumed that since the increase in kidney weight showed a dose response relationship, and was detected in the absolute kidney weight at the mid-dose, but as both absolute and relative kidney weight at the high-dose, that the increase in kidney weight observed is related to renal toxicity. In addition, the developmental evaluation of the offspring from this study indicate a NOAEL at the mid-dose and reduced fetal body weight and increased incidence of skeletal variations at the high-dose. Developmental effects from ethylene glycol appear to be the result of maternal metabolic acidosis (Khera et al. 1991). It appears that in the mouse, the maternal kidney was the most sensitive indicator of those parameters evaluated. Of the available acute inhalation studies, Tyl (1988) had the highest NOAEL that was associated with a dose-related effect. It is notable that the LOAEL for maternal toxicity in this study is equal to the NOAEL for developmental toxicity in this study. Effects observed in humans suggest a similar MRL. For instance, in Wills et al. (1974), male volunteers experienced upper respiratory tract irritation after a 15-minute exposure to ethylene glycol in ambient air at 55 ppm; doses above 79 ppm were not tolerated.

Agency Contact (Chemical Manager): Ed Murray

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical name(s): Ethylene glycol
CAS number(s): 107-21-1
Date: December 1995
Profile status: Third Draft Post Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ]Intermediate [ ] Chronic
Key to figure: 48
Species: mouse

MRL: 2.0 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Tyl 1989

Experimental design: Timed-pregnant CD-1 mice were given ethylene glycol by gavage on Gd 6–15. Females were weighed, observed daily for clinical signs, and evaluated for water intake. At sacrifice on Gd 18, females were evaluated for body weight, gravid uterine weight, and liver and kidney weight. Kidneys from control and high-dose dams were examined microscopically. Uterine contents were evaluated. There were no significant effects on the number of corpora lutea per dam; the number of total, nonviable, or viable implants per litter;, or on sex ratio. Fetal body weights per litter were reduced only at 1,500 mg/kg/day. There was no increase in the incidence of individual or total external or visceral malformations in any group relative to the vehicle control. There was a significant increase in the incidence of two skeletal malformations (fused ribs or thoracic arches) in the 1,500 mg/kg/day group, and the incidences of pooled skeletal malformations and all malformations were significantly increased in this group as well. The incidence of total malformations per litter was also significantly increased at 500 mg/kg/day. There were no significant increases in individual external or visceral variations, or in pooled external, visceral or skeletal variations or in total variations. The incidences of 23 skeletal variations were increased in the 1,500 mg/kg/day group. One skeletal variation (bilateral extra rib 14) was also increased at 500 mg/kg/day.

Effects noted in study and corresponding doses: A dose-related increase in developmental toxicity was observed:

150 mg/kg/day EG = low dose (NOAEL)

500 mg/kg/day EG = mid dose (increased incidence of total malformations and one skeletal variation - bilateral extra rib 14; Serious LOAEL)

1,500 mg/kg/day EG = high dose (reduced fetal body weight, increased incidence of 2 skeletal malformations (fused ribs or thoracic arches), increased incidences of pooled skeletal malformations and all malformations, increased incidence of 23 skeletal variations)

Dose endpoint used for MRL derivation:

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: No conversion was used.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
No conversion was used.

Was a conversion used from intermittent to continuous exposure?
If so, explain: No conversion was used.

Other additional studies or pertinent information that lend support to this MRL: Other developmental studies have identified ethylene glycol as a developmental toxicant after oral administration in animals, which adversely affects the conceptus at levels that do not cause significant adverse effects in the maternal animal. In the cited study (Tyl 1989), the maternal NOAEL is 1,500 mg/kg/day, compared to a developmental NOAEL of 150 mg/kg/day. In mice, 750 mg/kg/day caused reduced litter size and increased incidence of skeletal malformations, but was a maternal NOAEL (Price et al. 1985). Neeper-Bradley (1990) detected an increase in skeletal malformations in rats treated orally with 1,000 mg/kg/day ethylene glycol on Gd 6–15, with a NOAEL for developmental effects of 500 mg/kg/day. The maternal NOAEL in that study was 2,500 mg/kg/day. Similarly, Price et al. (1985) determined a developmental LOAEL of 1,250 mg/kg/day (skeletal malformations) in rats treated orally during gestation, a dose that caused only a 17% decrease in body weight in the maternal dams. Thus, using oral exposure during the period of major organogenesis in the rodent (Gd 6–15), the developmental effects are the most sensitive end point.

Agency Contact (Chemical Manager): Ed Murray

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical Name:	Ethylene glycol
CAS Number:	107-21-1
Date:	December 1995
Profile Status:	Third Draft Post Public
Route:	[ ] Inhalation [X] Oral
Duration:	[ ] Acute [ ] Intermediate [X] Chronic
Graph Key:	65
Species:	Rat

MRL: 2.0 [X] mg/kg/day [ ] ppm

Reference: DePass et al. 1986a; Woodside 1982

Experimental design: Groups of 130 male and female rats were fed diets to achieve dosage goals of 0, 40, 200, or 1,000 mg/kg/day ethylene glycol for 24 months. Mortality, body weight, diet consumption, histopathological findings, and gross findings were monitored. No evidence of oncogenicity was found. High-dose males (1,000 mg/kg/day) died prior to the 18-month termination, with death attributable to oxalate nephrosis caused by ethylene glycol exposure. Calcium oxalate crystals were found in the urine of high-dose males and females at 12 months. Increased absolute and relative kidney weights were observed only in high-dose males at 12 months. At 12 months, high-dose males had chronic nephritis (including tubular dilation, and proteinosis, glomerular shrinkage, tubular cell hyperplasia, and chronic interstitial nephritis). These results were supported by hematological effects also reported in the same study. Males in the high-dose group had decreases in red blood cell (RBC) count, hematocrit, hemoglobin, and increases in neutrophils at 12 months. No effects were seen at the lower doses. Females had normal hematology. Males in the high-dose group had a 4-fold increase in (BUN) and creatinine at 12 months, but no changes were noted at lower dose levels. At 12 months, high-dose males showed increases in urine volume, and a reduction in urine specific gravity. The only change seen in the urinalysis of females at 12 months was a reduction in mean pH at the high-dose level. High-dose males exhibited a significant reduction in absolute and relative liver weight at 12 months. High-dose females, but not males, had mild fatty metamorphosis of the liver; organ weight was normal. Females had normal body weight gain; high-dose males had decreased weight gain at 12 months of treatment. Mineralization, but no other lesions and no other organ weight changes, was seen in heart, lungs, and stomach in males, but not in females.

Effects noted in study and corresponding doses: renal toxicity

200 mg/kg/day EG = mid dose (NOAEL)

1,000 mg/kg/day EG = high dose (100% mortality from oxalate nephrosis in males by 18 months; increased absolute and relative kidney weights in high-dose males at 12 months; males had chronic nephritis, including tubular dilation, and proteinosis, glomerular shrinkage, tubular cell hyperplasia, and chronic interstitial nephritis; calcium oxalate crystals in the urine of females)

Dose and endpoint used for MRL derivation:

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose?
If so, explain: No conversion was used.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

Other additional studies or pertinent information that lend support to this MRL:
Other chronic feed studies report higher NOAEL and LOAEL values than those reported for rats in DePass et al. (1986a) and Woodside (1982). In mice treated for 24 months (DePass et al. 1986a) no adverse effects were seen at the high dose (1,000 mg/kg/day) in either males or females. In NTP (1982), male B6C3F1 mice exhibited oxalate nephrosis at 3,315 mg/kg/day, degeneration of the centrilobular hepatocytes at 1,625 mg/kg/day, and a NOAEL for hepatic effects of 812.5 mg/kg/day ethylene glycol for 2 years. In the same study, females showed hepatic and pulmonary effects at 6,500 mg/kg/day, with a NOAEL of 3,250 mg/kg/day.

The EPA (IRIS 1995) assigned ethylene glycol a reference dose (RfD) of 2.0 mg/kg/day with an uncertainty factor of 100 based on a NOAEL of 200 mg/kg/day kidney toxicity in rats (DePass et al. 1986a). The chronic-duration MRL developed by the Agency for Toxic Substances and Disease Registry for ethylene glycol is not in conflict with the current RfD for ethylene glycol.

Agency Contact (Chemical Manager): Ed Murray

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical name(s): Propylene glycol
CAS number(s): 57-55-6
Date: December 1995
Profile status: Third Draft Post Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X]Intermediate [ ] Chronic
Key to figure: 1
Species: Rat

MRL: 0.009 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Suber et al. 1989

Experimental design: Young, healthy adult Sprague-Dawley rats were divided into 4 groups of 19 males and 19 females each. Three groups were exposed for 5 days per week, 6 hours per day for 13 weeks by nose-only inhalation to mean target aerosol concentrations of 51, 321, or 707 ppm propylene glycol. The fourth, the control group, was exposed to humidified, filtered room air. Nasal hemorrhaging occurred in all exposed groups of male and female rats indicating that propylene glycol can act as a dehydrogenating agent. From week 2–14, the average of nasal hemorrhaging in male rats was <1%, 64%, 74%, and 75% in controls, low-exposure, medium-exposure, and high-exposure groups, respectively. In females, the average indices were < 1% in controls, 14% in the low-exposure group, and 71% in the medium and high-exposure groups. Animals recovered during non-exposure weekend periods. Similar trends were observed for ocular discharge, with females having generally less ocular discharge than males. A significant reduction in body weight of 5–7% starting on day 50 and continuing until the end of the study was observed in female rats receiving the highest dose of 707 ppm propylene glycol. Similar observation was made in the group receiving 321 ppm of propylene glycol but later in the study starting on day 64. This body weight reduction was correlated with a significant reduction in food consumption beginning on study day 43 and 50 for the high- and medium-exposure females, respectively. Female rats exposed to 321 ppm propylene glycol had a significant decrease in white blood cell count and lymphocyte numbers. Female rats exposed to 707 ppm propylene glycol had a significant decrease in hemoglobin concentration, white blood cell count and lymphocyte numbers. Male rats in the medium (321 ppm) and high (707 ppm) groups had a significant decrease in serum sorbitol dehydrogenase and gamma-glutamyl transferase. A significant decrease in total serum protein was observed in male rats treated with high (707 ppm) dose of propylene glycol while females treated with a medium (321 ppm) dose of propylene glycol had an increase in total serum protein. These changes were considered as being sporadic. Kidney weight was decreased at 321 ppm in both sexes. Although there were no treatment-related gross pathology changes, light microscopy revealed thickening of respiratory epithelium with increase in the number of goblet cells and their mucin content in both female and male animals receiving medium and high propylene glycol dose. Minute volume, tidal volume, and respiratory rates were not significantly altered in rats exposed to 51, 321, or 707 ppm propylene glycol for 13 weeks, suggesting that animals adapted to the exposure concentrations.

Effects noted in study and corresponding doses: Nasal hemorrhaging was observed in all PG-treated groups:

51 ppm PG = low dose (64% in males, 14% in females; less serious LOAEL)

321 ppm PG = mid dose (74% in males, 71% in females)

707 ppm PG = high dose (75% in males, 71% in females)

Dose endpoint used for MRL derivation:

[ ] NOAEL [X] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [X] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: No conversion was used.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
Doses were converted from mg/L to ppm:

0.16 mg/L x 1,000 = 160 mg/m^3. 160 mg/m^3 x 24.45/ 76.09 (MW PG) = 51.4 ppm

1.0 mg/L = 321.3 ppm

2.2 mg/L = 706.9 ppm

Was a conversion used from intermittent to continuous exposure?
If so, explain: Animals were exposed for 6 hours per day, 5 days per week. Since the effect (nasal hemorrhaging) subsided when exposure was discontinued during the weekend periods, it seemed relevant to adjust the exposure period not only to a continuous 24 hour, but also to a 7-day exposure. Therefore conversion factors of 6/24 and 5/7 were used:

51 ppm x 6/24 x 5/7 = 9 ppm

Other additional studies or pertinent information that lend support to this MRL: This was the only suitable intermediate-duration inhalation exposure study available.

Agency Contact (Chemical Manager): Ed Murray

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-l) 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer endpoints, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are'limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15 to 364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a lmown length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-l).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.4 , "Relevance to Public Health," covers the relevance of animal data to human toxicity. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to ethylene glycol and propylene glycol via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment ‚Group's upper-bound estimates'of the slope of the cancer dose response curve at low dose levels (q_l*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 →

TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
					↓		
Cancer							
38	Rat	18 mo 5d/wk 7hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

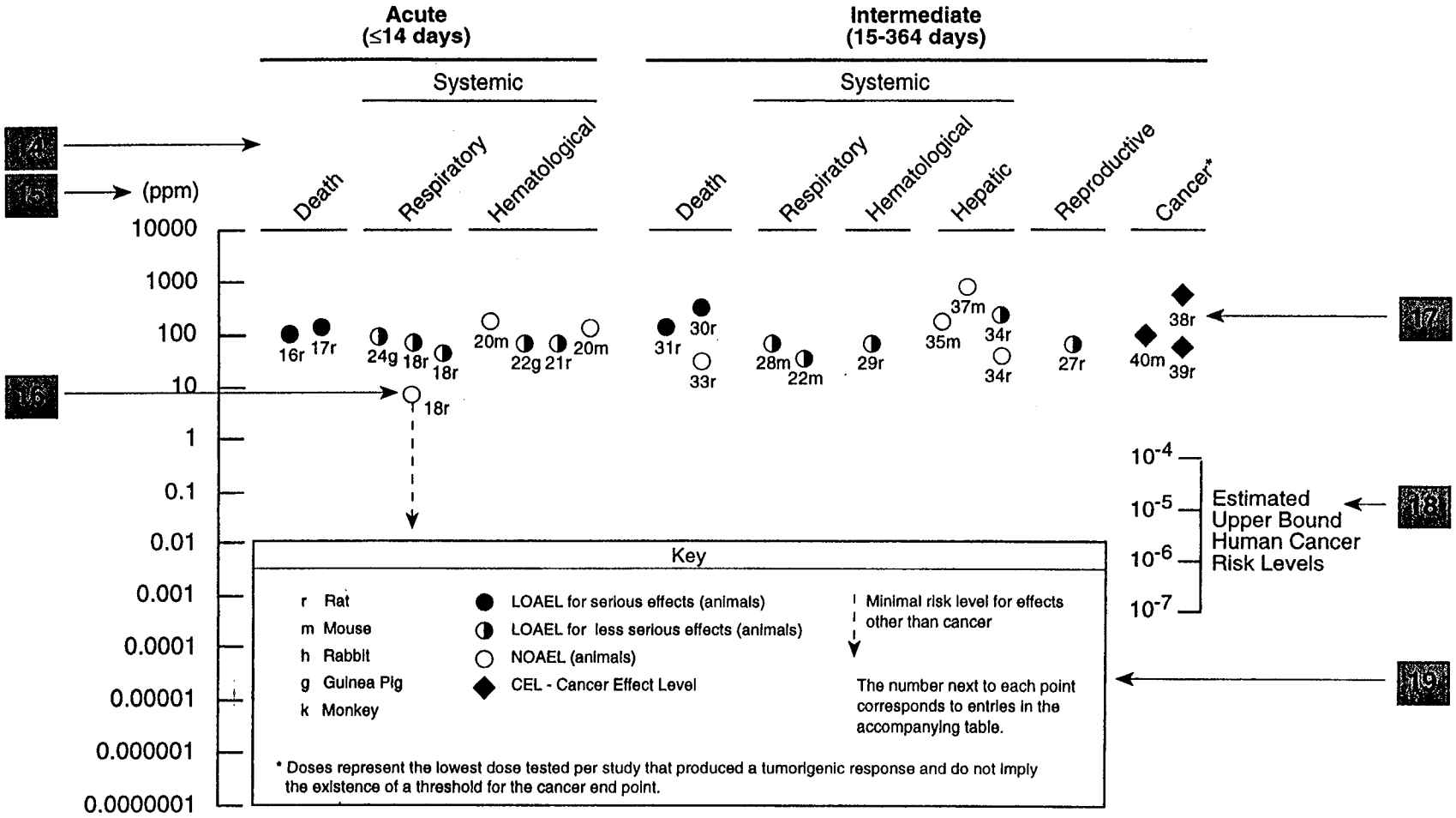
[a] The number corresponds to entries in Figure 2-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation



APPENDIX B

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions.

1. What effects are known to occur in humans?

2 . What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers endpoints in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer endpoints (if derived) and the endpoints from which they were derived are indicated and discussed.
Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.4, “Relevance to Public Health,” contains basic information lmown about the substance. Other sections such as 2.6, “Interactions with Other Chemicals”, and 2.7, “Populations that are Unusually Susceptible” provide important supplemental information.

APPENDIX B

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (IF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
Dl	deciliter
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient

K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
Mosm	milliosmolal
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange

SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram